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ERA-EDTA Operative Headquaters
Via XXIV Maggio, 38 – 43123 Parma, Italy

Issue #1 June 13th

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GEORGE S. REUSZ

Budapest, Hungary
President of the
56th ERA-EDTA Congress

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What are current challenges that Hungarian nephrologists face?
Probably the same ones as are faced in all the other European countries – the buzzwords being demographic change and the scarcity of young doctors. Confronted not only with an ageing society, but also with a rising incidence of common diseases such as diabetes and high blood pressure that can lead to kidney failure, we are anxious about a significant increase in nephrological patients. Making kidney disease more 'perceptible' among the population and raising people's awareness of preventive measures is one challenge.

The second is that nephrology no longer appears to be as attractive a discipline for young doctors. After the collapse of the socialist regime, many young physicians went into nephrology and discovered it for themselves. In those days, nephrology exerted a considerable attraction: physicians and nursing staff experienced that they could save the lives of human beings whom they were previously unable to treat and who died as a result. Treating patients successfully and experiencing that success engenders an enthusiasm for the discipline among young doctors and imparts a high level of meaningfulness to their own activity. Nowadays it is almost taken for granted that we save lives day in, day out, with dialysis. The innovatory nature of the discipline is no longer seen and appreciated in that form, even though nephrology is still the only medical speciality that is able to artificially replace the functions of the organ for years and even decades and save those concerned from an otherwise certain death. Despite that, young doctors are drawn more towards intensive medicine, gastroenterology or oncology which are perceived as more innovative because they conduct more studies and test new, targeted therapies. We have some catching up to do here – it is essential that we re-awaken a genuine enthusiasm for nephrology. Our speciality, too, has many innovations to offer, but we have to work harder on how we present ourselves to the outside world.

Another aspect that exacerbates the problem of attracting the next generation of doctors to nephrology here in Hungary is the payment for providing dialysis. This had not changed over

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'Nephrology is an innovative discipline – we just don't emphazise that enough'

An interview with Professor George Reusz, congress president of the 2019 ERA-EDTA Congress.

Professor Reusz, we are delighted to be welcomed by you as our host here in Budapest. The last ERA-EDTA Congress held in Budapest was back in 1986. There has been much change since then – in the political domain, in society and also in medicine – so to what extent has nephrology also been changed in these years?

The last time the ERA-EDTA Congress was held in Budapest was during the socialist era. We had an economy of scarcity in which many patients did not receive the essential medical care they needed, such as dialysis. A special committee decided which patients we were allowed to put on dialysis, and which not. There was not enough material, not enough machinery – everything was highly rationed. Older people, for example – and by that I mean people over 50 –, or people with other diseases and poor prognoses, did not receive dialysis as a rule. A situation like that is almost impossible to imagine nowadays! Today, we have the same high standards of medicine as in other European countries. We can give dialysis to any patient that needs it and wants it, namely with state-of-the-art technology and medication. The change in political system was a godsend as far as care of people with kidney disease was concerned – but also, of course, in many other areas of life.

What is the current situation in Hungary with regard to dialysis?

The dialysis centres in Hungary mainly operated by three international players – B. Braun, Diaverum and Fresenius. The state bears the costs of dialysis treatment, so patients don't have to pay anything. For people who experienced rationing of essential medical care, that is an enormous step forward and a key achievement of the social welfare state. The level of care provided nowadays is very good – we now have 52 dialysis centres in Hungary, and many nephrological wards have also been created by hospitals since the transition.

Yet sometimes I think that we have lost the holistic perspective. We have the best technology, but save on personnel. For example, every paediatric nephrology ward used to have psychologists who looked after not only the child, but also the whole family. In Europe, we treat patients at the highest medical level, but we might not provide enough psychosocial support, and that applies across all disciplines in medicine. But people consist of body and soul, and every illness ultimately affects both dimensions – although that is just a secondary aspect here. Kidney transplantations, the best form of renal replacement therapy from the medical perspective, are performed in Hungary, too, of course. They give patients many personal benefits and are also cost-efficient.

What are current challenges that Hungarian nephrologists face?

Probably the same ones as are faced in all the other European countries – the buzzwords being demographic change and the scarcity of young doctors. Confronted not only with an ageing society, but also with a rising incidence of common diseases such as diabetes and high blood pressure that can lead to kidney failure, we are anxious about a significant increase in nephrological patients. Making kidney disease more 'perceptible' among the population and raising people's awareness of preventive measures is one challenge.

The second is that nephrology no longer appears to be as attractive a discipline for young doctors. After the collapse of the socialist regime, many young physicians went into nephrology and discovered it for themselves. In those days, nephrology exerted a considerable attraction: physicians and nursing staff experienced that they could save the lives of human beings whom they were previously unable to treat and who died as a result. Treating patients successfully and experiencing that success engenders an enthusiasm for the discipline among young doctors and imparts a high level of meaningfulness to their own activity. Nowadays it is almost taken for granted

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that we save lives day in, day out, with dialysis. The innovatory nature of the discipline is no longer seen and appreciated in that form, even though nephrology is still the only medical speciality that is able to artificially replace the functions of the organ for years and even decades and save those concerned from an otherwise certain death. Despite that, young doctors are drawn more towards intensive medicine, gastroenterology or oncology which are perceived as more innovative because they conduct more studies and test new, targeted therapies. We have some catching up to do here – it is essential that we re-awaken a genuine enthusiasm for nephrology. Our speciality, too, has many innovations to offer, but we have to work harder on how we present ourselves to the outside world.

Another aspect that exacerbates the problem of attracting the next generation of doctors to nephrology here in Hungary is the payment for providing dialysis. This had not changed over

The Congress Organising Committee is very pleased to announce the Run for Kidneys 2019 event which will take place on June 14, 2019 at 4.30 p.m. during the 56th ERA-EDTA Congress at Hungexpo-Budapest.

The Run for Kidneys 2019 proceeds will be donated directly to the Hungarian Nephrology Foundation.

Schedule:

1 p.m.	*Opening of the Run Centre*
4 p.m.	*End of on-site registration*
4.15 p.m.	*Opening ceremony & warm up*
4.30 p.m.	*Start of the 5 km run*
5.15 p.m.	*Announcement of results*

(On-site registration closes 30 minutes before the start of the given race)

On-site registration: Entry Hall III - Open on June 13, 2019 from 8 a.m. to 6 p.m. and on June 14, 2019 from 8 a.m. to 1 p.m.

The on-site registration can only be settled by cash payment. The registration fee is 20€. The on-site registration package does not include the unique cotton t-shirt made for the event.

Get fit, challenge yourself and raise awareness for an important issue. For you it's just a Friday afternoon but for somebody it's the chance to heal. Stay tuned and support your charity run during the Congress.

a long time, which made Hungarian centres less attractive internationally for doctors and specialised nursing staff, simply because they got paid relatively low salaries. It was also the reason why many specialists trained in Hungary left the country to work elsewhere. Some have returned, also because there has been a rise in salaries – and, of course, Hungarian nephrology is enriched by the international experience of those who return!

Let's come back to the innovational nature of the speciality – is nephrology treading water?

No, not by a long shot. A lot has been achieved in recent years, especially, if you just think of complement inhibition, various enzyme therapies for treating rare diseases, or monoclonal antibodies against various interleukins, which are currently in the early phase of clinical testing. These are interesting new approaches – we just have to publicise them more and communicate them to the outside world. This is why the banner for this year's congress is 'Precision Nephrology – what we know, what we think we know and what we need to know'. The aim of precision medicine is to develop individually tailored strategies and therapies for treating patients – or as Barack Obama once said, 'delivering the right treatments, at the right time, every time to the right person'. The latest successes achieved by molecular genetics, and the improvements in sequencing and analysing DNA base pair by base pair are among the driving forces behind these advances. We are now obtaining some early indications from major international genome studies of the specific gene mutations that favour the development of kidney disease, so this is a broad area of research for young nephrologists.

Nephrology is still an innovative discipline – again: we just don't emphasize that enough. One example I would like to mention is SGLT2 inhibition, the renoprotective potential of which has been investigated by Prof Christoph Wanner, among others. We have been looking for a long time for therapies for halting progressive CKD, and it looks as if we have now achieved an important milestone. And it is not as if dialysis techniques have not advanced further. Progress in that area happens in small, steady steps, but if you compare the technology of 20 years ago with today's, you can see just how innovative we have actually been. No-one would accuse the car industry of being short on innovation merely because cars still run on four wheels and are powered by an internal combustion engine. Progress in terms of speed, safety, convenience and also improvement of the eco-balance is recognised as innovative by everyone who is interested in cars. However, we have also achieved precisely that kind of progress in the field of dialysis technology, too, and we should not play it down.

What role does ERA-EDTA play in 'precision nephrology' and 'innovative research'?

A crucial one, because it defines standards of quality and enforces them throughout Europe. The 'European Renal Best Practice' (ERBP) Guidelines establish evidence-based standards for diagnosis and therapy. This enables precision nephrology to take a major step forward. It has also provided enormous support for research – just think of the many working groups with international composition that have published pioneering papers, or the initiation of major research projects. Or think of the high-quality training programs, and above all the ERA-EDTA Congress. I believe that this year's Congress in Budapest will also give a further boost to Hungarian nephrology, because in the final analysis, such a major event shows the next generation of doctors that nephrology is a key 'player' within the health system.

What are the highlights at this year's Congress, from your point of view?

Well, there's an incredible number of them – and my role as president of the Congress makes it even more difficult to pick out specific sessions. However, I would like to draw attention to the four plenary lectures to be held by highly-renowned experts from the U.S.A.: Rafael Yuste, from New York, will be giving a lecture on emergent diseases, while Sanjay Jain from St. Louis will speak about the interface of molecular mechanisms, pathology and genetics of developmental kidney diseases. The third plenary lecture on single-cell transcriptomics in kidney disease will be given by Katalin Susztak, Philadelphia, and the fourth on the transition from pre-dialysis to renal replacement therapy by Csaba P. Kovesdy from Tennessee. I should like to stress that the latter two speakers are both of Hungarian origin and that they started their careers in medicine here – Prof. Kovesdy in Pécs and Prof. Susztak at my alma mater, the Semmelweis University in Budapest.

Another part of the programme deserving special mention is the 'special track' on global and regional perspectives. This will include a series focusing on Hungary, with the title 'Nephrology: The Hungarian Perspective', which I am looking forward to immensely. This special track within the program will broaden the perspective, and another session, for example, will discuss general, transboundary challenges in nephrology. What I also find attractive is the new concept of 'Continuous Education and Professional Development' (CEPD), which is a separate pre-congress day when CME courses will be offered at the highest level on all the relevant topics within nephrology, in concentrated form and at one location.

Aside from the congress, what does Budapest offer its visitors?

Budapest is a wonderful, beautiful city, especially in early summer. You have a fantastic view over the city from the castle or the Citadella. There are also some very beautiful baths – the Gellert thermal bath, built in Art Nouveau style, is particularly famous. The city has many important galleries and museums, and the Museum of Fine Arts is showing the exhibition on 'The Triumph of the Body – Michelangelo and Sixteenth-century Italian Draughtsmanship' until the end of June. The Hungarian National Gallery in Buda Castle is always worth a visit, too. On top of that, there is a thriving nightlife scene in Budapest, where diners can enjoy both dinner and live jazz.

I really hope that the congress delegates will enjoy their stay in our wondrous capital and will find the Congress to be of great interest. ◘

INSTITUTIONAL

Visit the ERA-EDTA Shop and help us help!

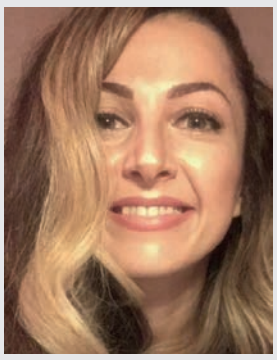
Shopping for a good cause is more popular than ever, and there has never been a better way to do it. Buy gifts for your family and friends at the ERA-EDTA Shop, and support young nephrologists at the same time. Last year, the shop raised enough money to fund travel grants for three young colleagues to attend the 56th ERA-EDTA Congress in Budapest this year.

"For graduate students, young doctors and researchers, conference travel grants are a terrific way to attend prestigious, career-defining conferences and I am very happy that I received a grant to travel to this year´s ERA-EDTA-congress. Apart from the career aspect it is thrilling to be in Budapest and experience the cosmopolitan flair of an international congress", says Berfu Korucu, Turkey. Ehab Al-sodany, Sweden, adds: "I am honored to be one of the recipients of a travel grant. For me, it was a great opportunity to attend one of key congresses of nephrology – and I thank all people who went shopping at the ERA-EDTA shop last year!" Sharma Pravesh from India comments: "Thanks to the grant I am able to share my research results with a broad international audience, which is very exciting for me."

"And indeed, this help has been made possible by the generous support from all the congress delegates, who bought nice things at our shop", explains Monica Fontana, Executive Manager at ERA-EDTA. "This year, we continue this initiative and we hope that we will be able to give more grants in 2020."

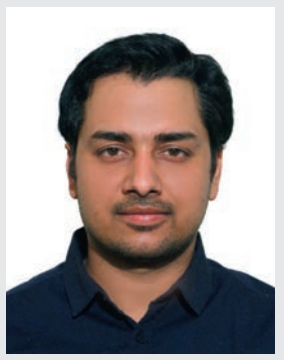
So why not ditch the guilt, and enjoy shopping now? ◘

Watch the interviews with the grant winners 2019 on the ERA-EDTA Youtube channel!



BERFU KORUCU
Turkey

EHAB AL-SODANY
Sweden



SHARMA PRAVESH
India

EDUCATION

Chronic TCMR: Banff update

MARION RABANT
Paris, France

The category of 'chronic active T-cell-mediated rejection' (chronic TCMR) appeared for the first time in the Banff 2005 meeting report [1] and was defined as 'chronic allograft arteriopathy'; i.e. arterial intimal fibrosis with mononuclear cell infiltration in fibrosis and formation of neo-intima. However, in recent years, several studies raised the question of the importance and the value of inflammation in scarred areas. In 2009, Mengel and al introduced the concept of total inflammation (ti); i.e. inflammation within the total cortex (scarred and unscarred). In this study, the ti-score showed stronger correlations with microarray-based gene sets representing major biological processes during allograft rejection, and was superior to the Banff i-score in predicting graft survival (AUC = 0.81 versus 0.65, p = 0.012) [2]. Independently, the DeKaf study in 2010 focused more precisely on inflammation only in fibrotic areas or 'i-IFTA' and showed a strong association between the severity of i-IFTA and graft loss, far stronger than of IFTA alone [3].

During the last Banff meeting in Barcelona in 2017, two studies on i-IFTA were presented. The Paris Transplant Group reviewed 1,477 one-year protocol biopsies in order to find the determinants and the prognosis of i-IFTA. In this cohort, 893 one-year protocol biopsies had IFTA, among which 518 had i-IFTA 0 (58 %), 181 i-IFTA 1 (20.3 %), 101 i-IFTA 2 (11.3 %) and 93 i-IFTA 3 (10.4 %). Patients with severe i-IFTA (i-IFTA 2 and 3) at one year had a significantly worse graft survival compared to patients with i-IFTA 0 or 1 (p < 0.0001). The determinants of i-IFTA at one-year in a multivariate model were previous episodes of TCMR or previous episode of BK virus nephropathy as well as under-immunosuppression [4]. At the same time, Nankivell et al quantified the i-IFTA in 1,220 IFTA biopsies from a cohort of 2,481 biopsies performed in 362 kidney-pancreas recipients to determine its prevalence, time course, and relationships with TCMR, immunosuppression, and outcome. Sequential histology demonstrated that i-IFTA was preceded by cellular interstitial inflammation and followed by IF/TA. Moreover, the one-year i-IFTA intensity correlated with early TCMR, the number of prior TCMR episodes and use of antithymocyte therapy [5].

Taken together, these findings suggested that i-IFTA, at least in many instances, was related to previous TCMR episodes and to chronic under-immunosuppression, and thus could represent chronic TCMR. Finally, after the Banff 2017 meeting, new criteria for chronic active TCMR were proposed based on three elementary lesions: the ti-score, the i-IFTA-score and the tubulitis t-score in non-severely atrophic tubules (Table 1) [6], after excluding other diseases known to be associated with i-IFTA (e.g. BK, antibody-mediated rejection, glomerulonephritis, obstruction) and representing chronic active TCMR grades IA and IB. Chronic active TCMR grade II remains 'chronic allograft arteriopathy' even if the last Banff classification specifies that "it should be noted that these arterial lesions may be indicative of ABMR, TCMR, or mixed ABMR/TCMR". Chronic allograft arteriopathy and accelerated arteriosclerosis have indeed been associated with ABMR and circulating donor-specific antibodies in several studies.

In summary, new histological criteria for the diagnosis of chronic TCMR grade IA, IB and II have been proposed after the 2017 Banff meeting based on the i-IFTA score, the ti score, tubulitis in non-severely atrophic tubules and the chronic allograft arteriopathy lesions (Table 1). These criteria need to be validated by prospective studies. Moreover, the management of such diagnosis should also be discussed and evaluated in prospective trials. ◘

Grade	Elementary lesions	Banff lesions
Chronic active TCMR Grade IA	Interstitial inflammation involving > 25 % of the total cortex **and** > 25 % of the sclerotic cortical parenchyma **with** moderate tubulitis involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out (BK, ABMR, GN, obstruction)	**ti2 or ti3 + i-IFTA 2 or i-IFTA 3 + t2**
Chronic active TCMR Grade IB	Interstitial inflammation involving > 25 % of the total cortex **and** > 25 % of the sclerotic cortical parenchyma **with** severe tubulitis involving 1 or more tubules, not including severely atrophic tubules; other known causes of i-IFTA should be ruled out (BK, ABMR, GN, obstruction)	**ti2 or ti3 + i-IFTA 2 or i-IFTA 3 + t3**
Chronic active TCMR Grade II	Chronic allograft arteriopathy (arterial intimal fibrosis with mononuclear cell inflammation in fibrosis and formation of neointima)	**cv**
No Borderline or suspicious category for chronic active TCMR		
A biopsy fulfilling the diagnostic criteria for chronic active TCMR should not be given a second diagnosis of Borderline or acute TCMR		

Table 1: Criteria for chronic TCMR from Ref [6]

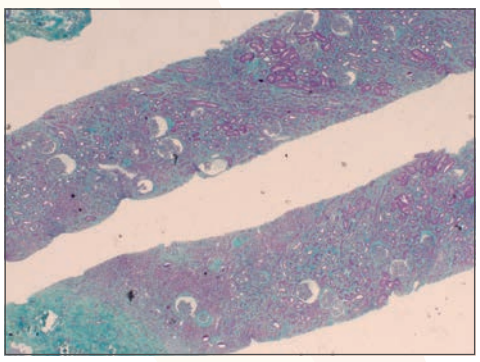


Figure 1: Masson Trichrome. X25. Allograft kidney biopsy with inflammation within scarred parenchyma © Marion Rabant

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CEPD 7
Nephropathology course
Thursday, 08.45–17.00, Hall A3

EDUCATION

IgA nephropathy New studies add important information to the debate

ROSANNA COPPO

Turin, Italy

IgA nephropathy (IgAN) (Figure 1) is a common glomerular disease, with some known features (Table 1). New studies published on therapeutic approaches have added important information and raised great debate.

The large cohort of 1,147 caucasian patients with IgAN observed in the European Validation of the Oxford Classification of IgA Nephropathy (VALIGA) study [1,2] allowed the comparison of two groups of 184 patients selected by a propensity score, perfectly matched for histologic and clinical features. Patients treated with corticosteroids (CS) and renin-angiotensin system blockers (RASB) had better outcomes for renal function survival and decrease in proteinuria during follow-up compared with matched patients with RASB alone.

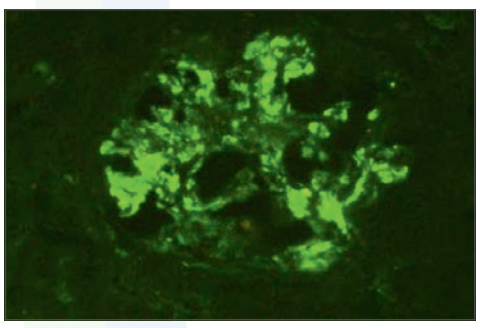

Figure 1: IgA nephropathy © Rosanna Coppo

The STOP-IgAN randomized controlled trial (RCT) [3] did not demonstrate a superior effect of CS/immunosuppressive therapy when added to comprehensive supportive care in patients with IgAN, proteinuria > 0.75 and < 3.5 g/d, and eGFR > 30 ml/min. The primary endpoint after three years was full clinical remission or decrease in eGFR > 15 ml/min. Patients with proteinuria resistant to six months of intensive supportive care (SUP) with a protein- and salt-controlled diet and RASB optimization were enrolled. They were randomized to SUP or CS for six months if eGFR was > 60 ml/min, or if eGFR was > 30 and < 59 ml/min, to cyclophosphamide for three months followed by azathioprine in addition to oral prednisolone, tapering over 36 months.

At the end of three years, full clinical remission was significantly more frequent in the immunosuppression group, but no difference between the two groups was found for protection from GFR decrease. The patients enrolled had a very limited renal function decline (−1.6 ml/min/year), rendering it difficult to prove the benefits of any additional treatment after a relatively short follow-up. A recent focused re-analysis of patients with immunosuppressive treatment showed greater benefits in the CS monotherapy group in comparison to the associated immunosuppressive treatment group, but without impact on renal function protection and with relevant side effects.

The Therapeutic Evaluation of Steroids in IgA Nephropathy Global (TESTING) [4] study was designed for patients with IgAN and proteinuria > 1 g/day in spite of three months of optimized RASB supportive care, who were randomized to oral methylprednisolone or placebo for two months, then weaning over six months. After two years, recruitment was discontinued because of excess serious adverse events (mostly infections, including two deaths) in patients in the methylprednisolone group. The primary renal outcome of progression was significantly more frequent in the placebo group. Although the results were consistent with potential renal protection of CS, definitive conclusions could not be made, owing to early termination of the trial. Interest is now focused on the ongoing TESTING Low Dose trial (ClinicalTrials.gov NCT01560052), with the hope of a reduction of side effects while maintaining the clinical benefits of CS.

The NEFIGAN phase 2 trial [5] used a new enteric controlled-release formulation of the corticosteroid budesonide (TRF budesonide) targeted to the Peyer's patches at the ileocecal junction. TRF budesonide was compared with placebo in patients with persistent proteinuria despite optimized RASB. At nine months, proteinuria had decreased more significantly and eGFR was stabilized in TRF budesonide-treated patients. No increase in serious adverse events and infections was reported.

In other recently published trials of immunosuppressive treatments in IgAN, rituximab failed to prove any benefit for renal function and proteinuria in a small RCT. Some recent pilot studies have reported a reduction in proteinuria in a few patients on new experimental drugs, including proteasome inhibitors, hydroxychloroquine and complement inhibitors. Indeed complement inhibition represents one of the areas of major interest for future therapeutic approach in patients with IgAN. ◘

1. Frequency particularly high in Asia (39 %) and Europe (22 %)
2. Genetic background (accounting for 6–7 % overall risk)
3. Mucosal immune system abnormal synthesis of Galactose deficient IgA1 (Gal deficient IgA1) and multi-hit pathogenesis with IgG anti deGal-IgA1
4. Risk factors at renal biopsy: reduced GFR, proteinuria, hypertension
5. Renal pathology features (MEST score) as independent risk factor for progression
6. Persistent proteinuria > 1 g/day over years of follow-up as major risk factor for progression
7. KDIGO 2012 :Therapy based on renin-angiotensin inhibition (RASB)
8. Corticosteroid in RASB resistant cases

Table 1: Known features of IgA nephropathy

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CEPD 1
Primary and Secondary GN, vasculitis and autoimmune diseases
Thursday, 08.45−12.25, Hall G1

EDUCATION

Update on tubular and tubulointerstitial diseases New insights from the laboratory and the clinic

DETLEF BOCKENHAUER

London, United Kingdom

In an average adult, the glomeruli each day produce a primary urine volume of about 150 liters, containing the equivalent of approximately 1.2 kg of salt, 150 g of sugar, aminoacids, smaller proteins, vitamins, further electrolytes and much more. All of this would be lost in the urine, if it were not reabsorbed by the tubules. This enormous task is accomplished by a whole orchestra of specialized transport proteins expressed in the epithelium of the tubule. Dysfunction in one or more of these transporters leads to specific defects in reabsorption, clinically characterized by the abnormal excretion of solutes, often with consequently altered blood levels.

Collectively, these disorders are referred to as tubulopathies and they can be inherited or acquired. The clinical spectrum ranges from life-threatening derangements of volume, electrolyte and acid-base homeostasis, associated growth failure and rickets to minor abnormalities, such as isolated loss of glucose. Many of these disorders are associated with polyuria, which can reach more than 10 liters per day.

In contrast, tubulointerstitial disease are characterized predominantly by progressive chronic kidney disease, which may be associated with abnormal tubular solute handling, especially of uric acid, leading to gout.

In this talk, I will focus on three main aspects:

1. Selected newly discovered tubulopathies and disease genes, most of which are associated also with extrarenal manifestations, which can provide important diagnostic clues and provide insights into the molecular basis of renal physiology.
2. Recent clinical insights that inform the management of these patients.
3. Selected interesting aspects concerning autosomal dominant tubulointerstitial diseases. ◘

CEPD 5
Genetic diseases and rare diseases
Thursday, 08.45−12.25, Hall A1

The new age of kidney imaging The role of super-resolution microscopy in diagnosis and research

NICOLE ENDLICH
Greifswald, Germany

Podocytes are characterized by their complex 3-D morphology, which is essential for an intact and size-selective filtration of the blood. The foot processes of this postmitotic cell interdigitate in a regular way with the foot processes of the neighboring podocytes. Between these interdigitating foot processes, a slit membrane is formed by the dimerization of the transmembrane protein nephrin. Changes in this typical morphology (like the broadening of the podocyte foot processes, the effacement) are associated with the loss of the size selectivity of the filtration barrier followed by proteinuria, the clinical hallmark of glomerulopathies. Therefore, the morphology of the podocyte foot processes is directly linked with the function of the filtration barrier.

In the past, to observe changes in the foot process morphology, scanning and transmission electron microscopy (EM) were the only available techniques, since the size of the foot processes is below the resolution limit of the light microscope. Therefore, analysis of the foot process morphology in health and disease was very time consuming and technically challenging, and quantification of the foot processes was extremely difficult. However, the development of new microscopic techniques, summarized under the term super-resolution microscopy, allows the visualization of podocyte foot processes by light microscopy. These new techniques have given the starting signal for a new age of kidney imaging.

Recently, our group has developed and established such a super-resolution imaging of podocyte foot processes by the use of structured illumination microscopy (SIM). SIM overcomes the optical resolution limit of the light microscope, which was postulated by Ernst Abbe, and allows an optical resolution of 85–100 nm. Moreover, we combined 3-D SIM with a quantification procedure named PEMP (podocyte exact measurement procedure), allowing a quick, exact and quantitative measurement of changes in the foot process morphology.

The technical preparation for PEMP is straightforward: in the standard histological routine, formalin-fixed and paraffin-embedded kidney sections of a thickness of 4 µm are transferred on to a normal microscopic glass slide and stained with an anti-nephrin antibody. This method is much quicker and simpler than the sophisticated preparation procedure for EM, where ultrathin sections of glutaraldehyde-fixed and Epon-embedded tissue of 50–100 nm thickness have to be transferred on to a grid with a size of 3 mm. Additionally, handling of the sections is much easier when using a light microscope in contrast to the EM.

The quantification of the foot process morphology can also be easily and quickly performed. PEMP measures the length of the slit membrane per glomerular capillary surface area of the stained kidney sections automatically, and instantaneously calculates the so-called FSD (filtration slit density), which gives an objective and exact value for each kidney.

By the use of biopsies of patients suffering from glomerulopathies, PEMP allows highly specific and personalized analysis of the severity of the disease. Furthermore, PEMP enables the quantification of the morphology changes over time, which would be highly supportive of transplantation follow-up examination. In contrast to EM, 3-D SIM makes possible the simultaneous detection of three and more proteins in super-resolution.

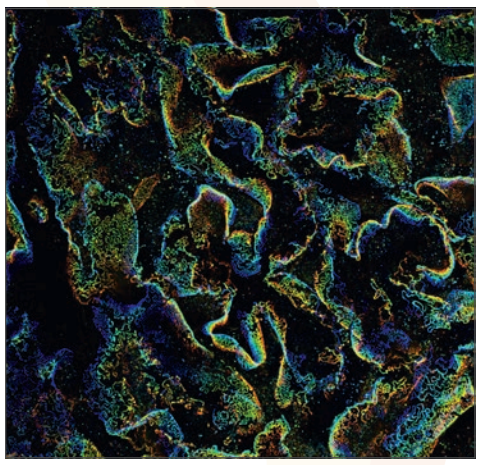

Figure: 3-D SIM of a nephrin-labelled glomerulus © Nicole Endlich

Taken together, the use of the super-resolution microscopy technique opens a new age of kidney imaging, which can be used for diagnosis as well as research purposes. ◘

CEPD 6
Basic and translational Nephrology
Thursday, 08.45–12.25, Hall A2

EDUCATION

Genomic studies in adult CKD patients Clinical sequencing can identify disease-causing mutations and unrecognized genetic causes

ALI G. GHARAVI

New York, NY, USA

In the past decade, advances in genomic technologies have empowered many discoveries in human genetics. These technologies are now being introduced into clinical care, facilitating diagnosis and management of patients. Genomic technologies are now routinely incorporated into clinical care for many pediatric and neurodevelopmental disorders, as well as cancer care. However, up until recently, the utility of these technologies in adult constitutional disorders such as chronic kidney disease (CKD) had not been systematically studied.

Multiple recent studies have demonstrated that application of clinical sequencing such as exome sequencing can identify disease-causing mutations and unrecognized genetic causes of kidney disease, with diagnostic yield ranging from 5 to 25 % depending on the underlying clinical diagnosis. These studies have illustrated the heterogeneity of genetic nephropathies: a recent study identified 66 different genetic diseases in 3,315 patients with nephropathy [1, 2, 3] (Figure).

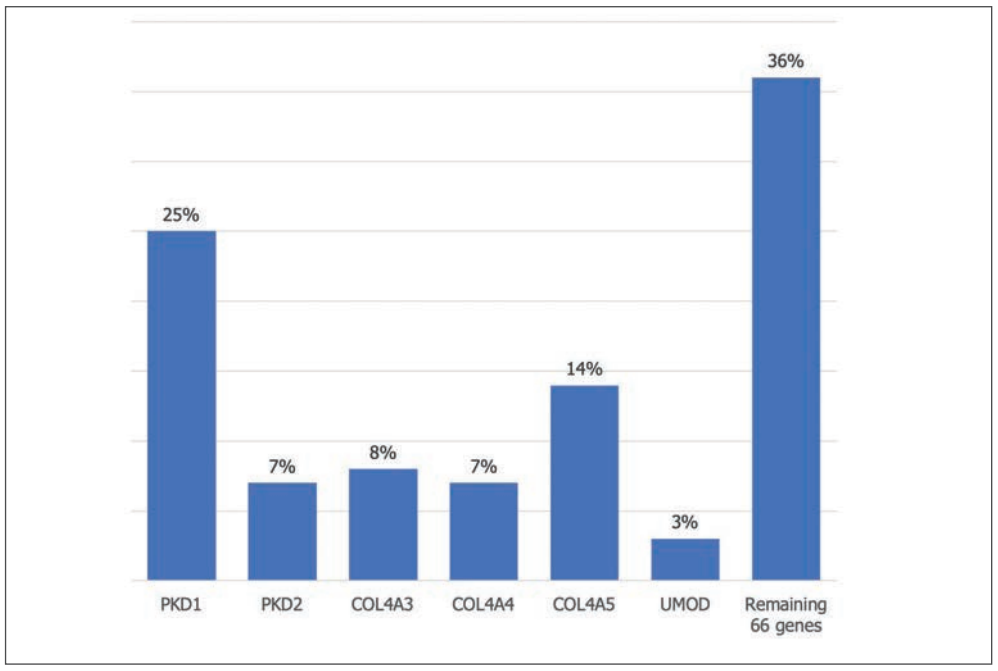

Figure: A recent study identified diagnostic mutations in 9.3 % of 3315 patients with nephropathy. Of the 66 distinct monogenic disorders observed, 6 genes collectively accounted for 63 % of the genetic diagnoses. © Ali G. Gharavi. Modified from: N Engl J Med 2019; 142–51

Notably, exome sequencing could also provide a diagnosis in patients with nephropathy of unknown cause, which constitute 10–15 % of patients with kidney failure. These findings promise a new era in kidney care, where genomics will be incorporated into practice to guide management, surveillance, therapy and family counseling. Nonetheless a number of challenges remain, such as interpretation of variants of unknown significance, proper incorporation of genetic information into health records and procedures for return of resultas. ◘

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CEPD 5
Genetic diseases and rare diseases
Thursday, 08.45–12.25, Hall A1

SGLT2 inhibition in CKD: Discussing the key questions and evidence

EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIRMAN

John Deanfield, MD
London, United Kingdom

AGENDA

09:45 – 09:50 **Introduction**
John Deanfield, MD – *London, United Kingdom*

09:50 – 10:05 **Outcomes of SGLT2i in Diabetic Kidney Disease: Is it all diabetes?**
Rajiv Agarwal, MD – *Indianapolis, IN, USA*

10:05 – 10:20 **The knowns and unknowns of SGLT2 inhibition in CKD**
Paola Fioretto, MD – *Padua, Italy*

10:20 – 10:35 **The clinical landscape of managing patients with CKD: Where are we now and what can we expect?**
Will Herrington, MD – *Oxford, United Kingdom*

10:35 – 10:45 **Discussion**
All faculty

FRIDAY, JUNE 14, 2019 | 09:30 – 10:45 HRS | HALL F1

Supported by an unrestricted educational grant from Boehringer Ingelheim / Lilly.

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INSTITUTIONAL

ERA-EDTA Ordinary Council Member Elections – the Candidates

Inga Arune Bumblyte – Lithuania

"I know actualities of small countries and I can contribute to making closer big and small European countries. I can contribute into the developing stronger relation between ERA-EDTA and the Baltic countries as well as Belarus and Ukraine."

Hans-Peter Marti – Norway

"My aims are to increase the awareness of the ERA-EDTA in the medical profession and in the general public, to ensure that nephrology continues to be an attractive discipline, and to work towards the establishment of a 'European Kidney Biopsy Registry'."

Mario Cozzolino – Italy

"I hope to help the Society with my background in both clinical nephrology and basic research area. I want to serve the Society by lending my advisory skills to organize the ERA-EDTA congress, educational meetings, and research strategies."

Gyorgy Reusz – Hungary

"I would like to strengthen the relationship between the ERA-EDTA and the National Societies. It is of crucial importance to recognize regional similarities, but also regional differences, and appreciate each other's activities."

Ronald Gansevoort – The Netherlands

"I would like to commit myself to getting more attention for screening for early CKD and prevention of CKD progression on a general population level. The message of early CKD as important risk factor must be spread across Europe."

Serhan Tuglular – Turkey

"Earthquakes and changing climate conditions require special attention. I would like to participate and increase ERA-EDTA's activities on this area. Besides, the application of femal candidates was encouraged."

EDUCATION

Optogenetic control of inflammation in AKI Defining new approaches to treat acute kidney injury

MARK D. OKUSA

Charlottesville, VA, USA

The nervous and immune systems have long been studied independently, however over the last few decades considerable advances have been made that indicate that these two systems are linked to maintain normal homeostasis, as well to respond to stress and pathophysiological disorders. Recent advances have identified neural pathways that regulate immunity and inflammation via the inflammatory reflex pathway, identifying specific molecular targets that can be modulated by stimulating neurons electrically.

Neuroimmunomodulation by non-pharmacological methods is emerging as a novel therapeutic strategy against inflammatory diseases including kidney disease. For example, electrical stimulation of vagus nerves or treatment with pulsed therapeutic ultrasound activates the cholinergic anti-inflammatory pathway and protects mice from acute kidney injury. Direct innervation of the kidney, including afferent and efferent neurons, may play a role in modulating and responding to inflammation in various diseases, either locally or by providing feedback to regions of the central nervous system that are important in the inflammatory reflex pathway.

Optogenetics refers to the use of both optics and genetics for controlling cells, typically neurons, which have been genetically manipulated to express light-sensitive opsins. These opsins include excitatory channelrhodopsin-2 (ChR2) and inhibitory halorhodopsin and archaerhodopsin (Figure). For example, ChR2, originally discovered from the green alga Chlamydomonas reinhardtii, is a nonselective cation channel and its gate is rapidly opened by the conformational change after blue light application (maximum activation at 470 nm). Optogenetic tools that enable selective stimulation of specific neurons have uncovered neural circuits in the brain that modulate kidney function via activation of the cholinergic anti-inflammatory pathway, and these techniques will be valuable in dissecting other neural pathways that control immunity and inflammation.

This talk will highlight studies that define neural circuits using optogenetics that control inflammation and that may serve as targets for therapy of kidney diseases. ◘

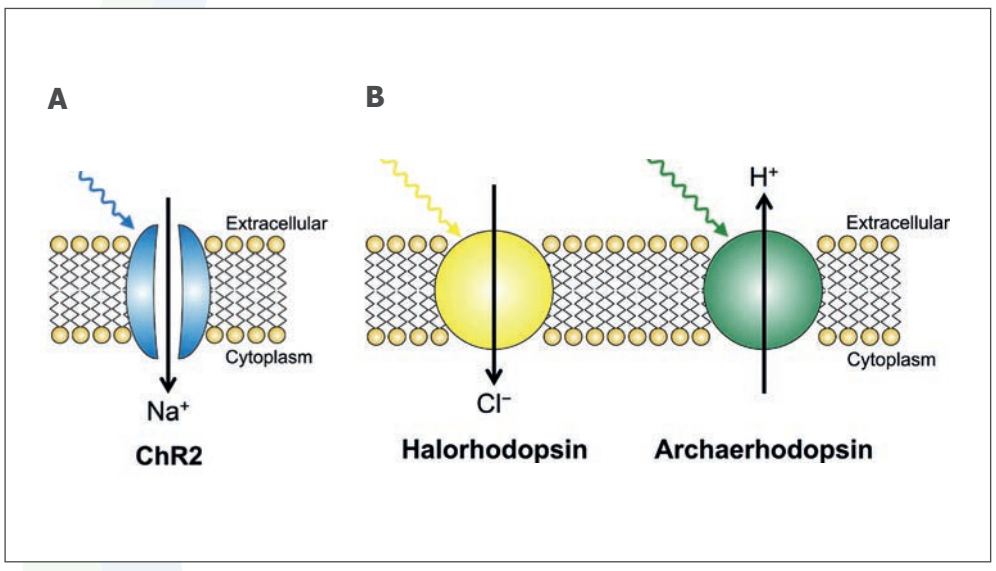
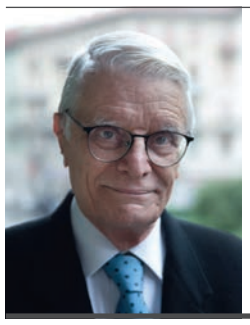


Figure: Schematics of an excitatory lightsensitive opsin, channelrhodopsin-2 (ChR2) CAVE (A), and inhibitory light-sensitive opsins, halorhodopsin and archaerhodopsin (B). The expression of these opsins does not affect the resting membrane potential because of the lack of ion flux without light application. (A) When ChR2 is illuminated with blue light, the gate of this nonselective cation channel is opened, which allows influx of Na+ and causes depolarization of the ChR2-expressing neurons. If the spike of Na+ entry is large enough for the membrane potential to reach the threshold, an action potential is evoked. (B) When halorhodopsin/archaerhodopsin is illuminated with yellow/green light, it functions as an inward Cl−/outward H+ pump and causes hyperpolarization of the neurons expressing these opsins, thereby exerting an inhibitory effect. From: Tanaka S, Okusa MD. Seminars in Nephrology. Semin Nephrol. 2019 Jan;39(1):85-95. doi: 10.1016/j.semnephrol.2018.10.008. Permission conveyed through Copyright Clearance Center, Inc.

CEPD 6
Basic and translational Nephrology
Thursday, 08.45–12.25, Hall A2

EDUCATION

Focal and segmental glomerular sclerosis Little progress in treatment of primary FSGS



CLAUDIO PONTICELLI

Milan, Italy

Focal and segmental glomerulosclerosis (FSGS) is a generic lesion with a variety of morphological variants and underlying etiologies and pathogenesis. There are several different clinical presentations of FSGS:

1. Primary FSGS (probably caused by unknown factors causing podocyte injury and increased permeability of the glomerular barrier).
2. Maladaptive FSGS (in which nephron losses caused by other diseases lead to chronic glomerular hyperfiltration and hypertension).
3. APOL1 nephropathy (due to variants of APOL1 gene in patients of African ancestry).
4. Familial or congenital FSGS (caused by mutation of genes encoding podocyte or slit diaphragm proteins).
5. FSGS associated with viral infection (mainly HIV)
6. Drug-induced FSGS (intravenous bisphosphonates etc).

It is important to differentiate primary from secondary FSGS. Primary FSGS is characterized by an acute or subacute onset, whereas proteinuria develops gradually in secondary FSGS. In primary FSGS, nephrotic syndrome is common, associated with hypoalbuminemia and severe proteinuria, while patients with maladaptive FSGS do not present with hypoalbuminemia and nephrotic proteinuria. In primary FSGS glomerulomegaly is uncommon and electron microscopy shows diffuse foot process effacement at kidney biopsy, whereas in secondary FSGS glomerulomegaly and segmental foot process effacement are common.

However, pathology cannot identify genetic abnormalities that are not uncommon. Next-generation sequencing to evaluate the presence of mutations of genes recognized >50 monogenic forms of steroid-resistant FSGS. A genetic analysis is suggested in young children (the risk of gene mutation is inversely related to age), in patients with steroid-resistant FSGS, in the presence of extra-renal signs and symptoms, in nephrotic patients of African ancestry (risk of APOL1 mutation), and in candidates for kidney transplantation (no risk of recurrence if FSGS is caused by genetic mutation).

Little progress has been made in recent years in the treatment of primary FSGS. The first-line treatment still rests on a prolonged administration of high-dose prednisolone. Some measures may be taken to reduce the incidence and severity of side effects. Short-acting corticosteroids should be preferred; the daily dose should be given in a single morning administration, and the drug-to-drug interactions of corticosteroids with other agents should be taken into account. The patient should be recommended to follow a low-calorie and low-sodium diet, undertake regular physical activity, and promptly report any side effects.

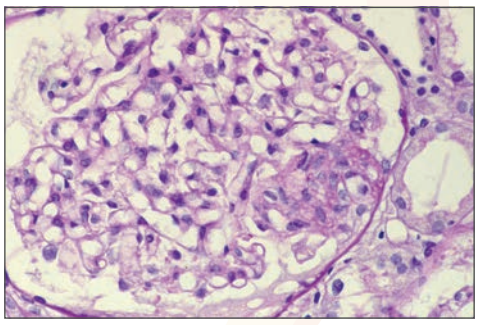


Figure 1: Focal and segmental glomerular sclerosis Courtesy of Dr Moroni Fondazione Ca' Granda IRCCS Ospedale Maggiore Policlinico di Milano

However, a number of patients do not respond and others cannot tolerate aggressive prednisolone therapy. Calcineurin inhibitors (CNI) are used as a second-line treatment. They can obtain partial or, more rarely, complete remission, but their impact on the long-term outcome of FSGS is still doubtful. Mycophenolate proved to be non-superior to CNI, and rituximab is effective in steroid-sensitive patients but few steroid-resistant adults with FSGS respond to rituximab. Preliminary studies have drawn attention to the possibility of using hydroxypropyl-βcyclodextrin, spansertan, etc.

Many studies are still needed to better classify the heterogeneous causes of so-called primary FSGS; to elucidate the pathophysiology of primary FSGS, to identify the impact of monogenic abnormalities in adults with FSGS; and to find new treatments able to obtain complete remission of proteinuria and to halt the progression to chronic irreversible lesions and end-stage renal disease. ◘

CEPD 1
Primary and Secondary GN, vasculitis and autoimmune diseases
Thursday, 08.45–12.25, Hall G1

Disorders of calcium and magnesium
The kidney plays a central role

PASCAL HOUILLIER
Paris, France

The renal handling of calcium and magnesium is a major determinant of plasma calcium and magnesium concentration, respectively. Both cations are filtered at the glomerulus and reabsorbed at specific places along the renal tubule; eventually, under normal conditions, only a tiny fraction of filtered calcium and magnesium is excreted in urine. Both cations are reabsorbed in part in the proximal tubule; however the main sites of controlled reabsorption are the cortical thick ascending limb of the loop of Henle, where calcium and magnesium are reabsorbed along the paracellular pathway, and the distal convoluted/connecting tubule, where calcium and magnesium are reabsorbed along the transcellular route via channels and transporters specific to each cation.

Calcium and magnesium reabsorption is enhanced by parathyroid hormone, both in the cortical thick ascending limb of the loop of Henle and in the distal convoluted/connecting tubule, and decreased by extracellular calcium and magnesium concentration in the thick ascending limb; the later involves the calcium/polycation-sensing receptor at the basolateral membrane of the cells. Nonhormonal factors, such as acidosis, decrease calcium and magnesium absorption in the distal nephron.

Many rare and more common diseases are able to alter the renal handling of calcium and magnesium. The diseases that primarily affect magnesium reabsorption in the distal tubule are not associated with a decrease in calcium reabsorption, hypercalciuria, renal stone disease and/or nephrocalcinosis; the likely reason is that calcium and magnesium reabsorption in the distal convoluted/collecting tubule uses distinct, ion-specific pathways. An example is Gitelman syndrome: patients with Gitelman syndrome often have hypomagnesemia and hypocalciuria. By contrast, in the cortical thick ascending limb of the loop of Henle, the driving force for reabsorption of both calcium and magnesium is the lumen-positive transepithelial potential difference; the permeability of the paracellular pathway to calcium and magnesium requires the expression of claudin 16 and claudin 19 at the tight junction. Consequently, both calcium and magnesium transport are affected under conditions of abnormal lumen-positive transepithelial potential difference or of low paracellular permeability to divalent cations. The diseases decreasing divalent transport in the thick ascending limb result in a renal loss of both calcium and magnesium, hypercalciuria and hypomagnesemia, nephrocalcinosis or renal stone disease. Because the potential difference primarily depends on active sodium chloride reabsorption, Bartter syndromes, type 1–4, are often associated with hypercalcuria and hypomagnesemia. Loss-of-function mutations of either *CLDN16* or *CLDN19* gene cause familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC), a severe autosomal recessive disease that often progresses towards end-stage renal failure: no renal loss of sodium chloride is found in patients with FHHNC. Finally, patients with mutations of the *CASR* gene, encoding the calcium/polycation-sensing receptor, have disorders of calcium and magnesium handling: the reabsorption is decreased in patients with gain-of-function mutations (autosomal dominant hypocalcemia) and increased in patients with loss-of-function mutations (familial hypocalciuric hypercalcemia). It is noteworthy that the most common of hypercalciuria in humans, the so-called idiopathic/genetic hypercalciuria is characterized, in part, by a defect in calcium reabsorption by the renal tubule. Beyond that, the pathophysiology remains poorly understood. ◘

CEPD 12
Electrolytes and urolithiasis
Thursday, 13.00–16.40, Hall A1

EDUCATION

Optimal timing and method for renal replacement therapy
A patient focus proposal

RAYMOND VANHOLDER

Ghent, Belgium

The questions about when to start renal replacement therapy (RRT) and about the preferred therapeutic option are seminal in view of the ever-rising patient numbers and the cost of renal replacement therapy (RRT). Regarding initiation, the IDEAL trial found no difference in mortality between chronic kidney disease (CKD) patients stratified to an early start (eGFR 10–15 mL/min/1.73 m^2) and those with a late start (eGFR 5–7). However, 75 % of those stratified to a late start initiated dialysis from the second year on, but has now disappeared after methodological improvements. Quality of life is better with PD and societal cost is lower, especially in high-income countries. A similar reasoning can be held for home HD versus in-center HD. When asked, patients prefer home dialysis, irrespective of their actual therapeutic situation. Yet, throughout Europe, home strategies are underrepresented.

An often-neglected therapeutic alternative is conservative or palliative treatment (no RRT in patients in whom this therapy would be justified if based on kidney function alone). This option might be considered, especially in case of frailty, which is frequent in the aging dialysis population. Survival advantage in the elderly with dialysis, if any, amounts to only a few months, and the time gain in favor of dialysis is largely spent in hospital and thus comes with a loss of quality of life.

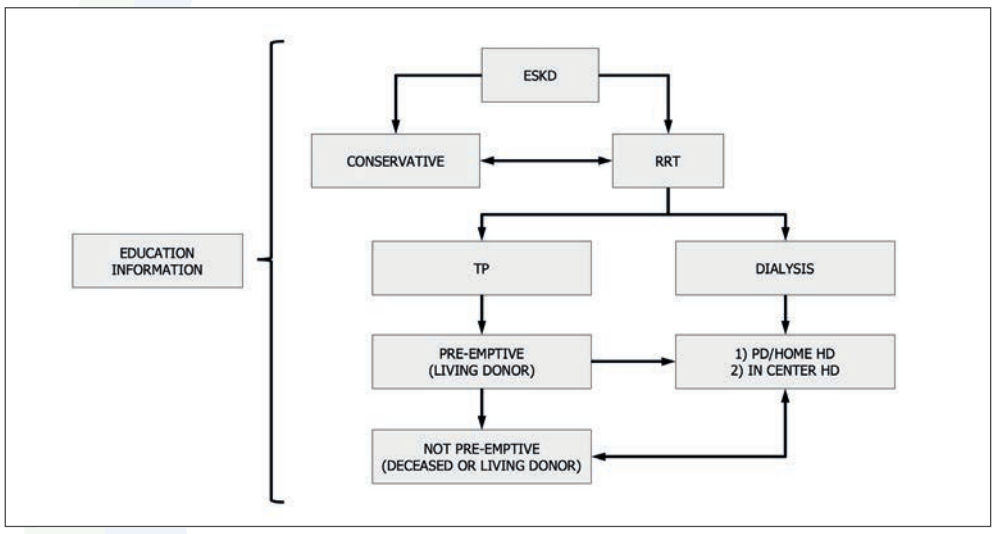


Figure: Flow chart of preferred strategies for renal replacement therapy © Raymond Vanholder

because of symptoms before they reached the threshold; hence the current recommendation to start dialysis when uremic symptoms develop, rather than relying on eGFR.

The question about the preferred strategy is more complex. RRT can be provided by hemodialysis (HD), peritoneal dialysis (PD) or kidney transplantation. When reviewing specific patient-related characteristics that may influence choice per individual, a number of objective factors help in defining the overall preference: survival outcomes, quality of life and societal cost. To this might be added ecologic impact, but current data are too scarce to allow in-depth discussion.

Kidney transplantation is far more cost effective than dialysis and quality of life is close to that of healthy subjects. Survival is superior to that of transplant candidates remaining on dialysis. Yet, dramatic differences in transplantation rates and in living versus deceased donation among countries suggest ample room for improvement, and a need for policy changes and education and quality programs to enhance transplant activity.

Among dialysis strategies, a survival disadvantage for PD versus HD was previously found

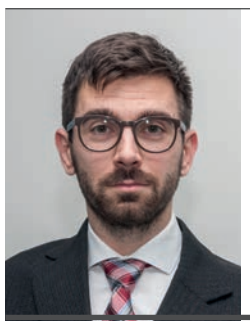
Throughout Europe, patients with end-stage CKD do not always receive their preferred therapy that assures the optimal quality of life. One element that could possibly impact patient choice is patient information and education, but enquiries reveal that many patients are dissatisfied with the information they receive, precluding a balanced choice. There is thus a need to organize specific programs with special focus on patient education.

Based on this information, a flow chart of preferred strategies for RRT can be developed (Figure), starting with the choice between conservative treatment and RRT. In the latter case, transplantation is the preferred option, if possible preemptive. When transplantation is temporarily or definitively impossible, dialysis is needed, with a preference for home strategies (peritoneal HD, home HD). If indicated, swift transition between all options must be possible. Decisions are to be made together with the patients and their next of kin, after full information. ◘

CEPD 2
Chronic Kidney Disease
Thursday, 08.45–12.25, Hall G2A

EDUCATION

Fibrillary glomerulonephritis and immunotactoid glomerulopathy
They have similar morphology, but a quite different pathogenesis



SÁNDOR TURKEVI-NAGY

Szeged, Hungary

Fibrillary glomerulonephritis (FGN), immunotactoid glomerulopathy (ITG) and cryoglobulinemic glomerulonephritis are characterized by Congo-red negative deposits organized ultrastructurally, derived from immunoglobulins. In our lecture we encompass the main features and differential diagnosis of FGN and ITG and we summarize the cases reported in university pathology departments in Hungary.

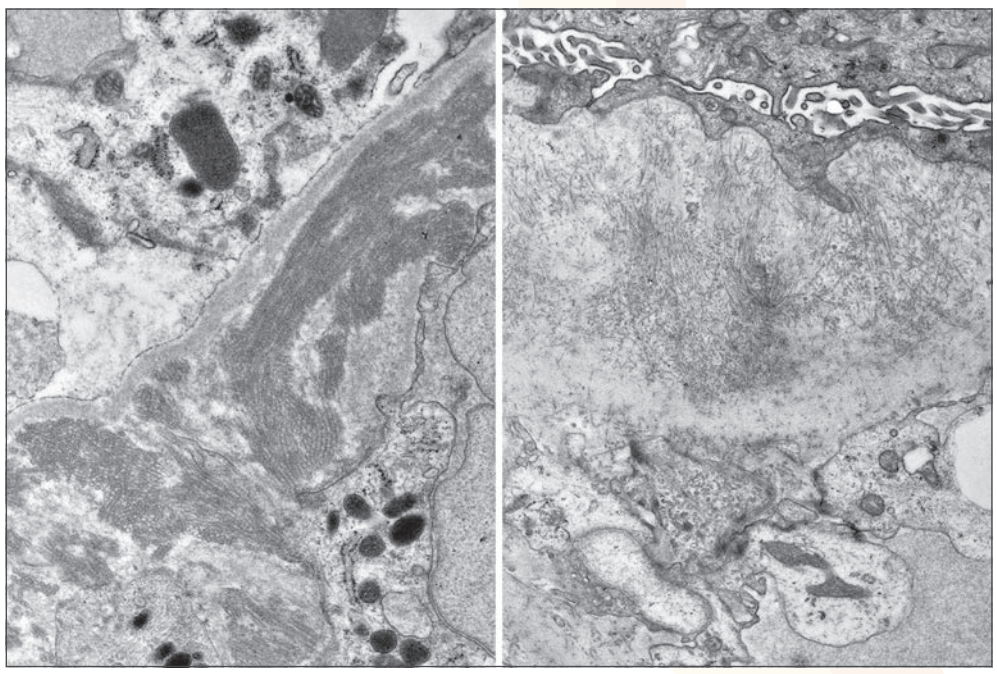


Figure 1 © Left: courtesy of Tibor Vas, Right: courtesy of Béla Iványi

FGN is characterized by the presence of amyloid-like fibrillar deposits, which are slightly thickened. Electron microscopy (EM) shows that they contain randomly oriented, non-branching fibrils with an average diameter of 20 nm with range 10–30 nm. Immunofluorescence (IF) reveals the presence of smudgy mesangial and peripheral IgG, C3c, usually polytypic light chains and IgG4 restriction. Light microscopy (LM) shows that the most common pattern has a silver-negative mesangial matrix expansion, which is Congo red-negative and weakly PAS-positive, with sclerosis or hypercellularity, and occasionally with membranoproliferative, membranous patterns. Some patients have HCV infection, but the pathogenesis is obscure.

For a differential diagnosis, the most challenging condition is amyloidosis [1]. In the majority of cases it can be overcome by applying an algorithmic approach [2], based on the results of silver and Congo-red staining and EM. However, several qualitative and quantitative features of the tissues, processing methods and stainings may affect the evaluability of the samples and, significantly, in a small number of cases the deposits are congophilic. Recently, a spectometric analysis identified a protein called DNAJB9, which can be detected immunohistochemically and has been shown to be a sensitive and specific biomarker of FGN even if other methods are equivocal [3].

ITG is defined by microtubules organized in parallel, which are Congo-red negative. EM shows that they have a diameter greater than 30 nm. IF reveals granular labeling with IgG and light chain restriction (usually kappa). As for pathogenesis, the condition is most probably monoclonal gammopathy-mediated and the majority of the patients have hematologic malignancy. The LM spectrum exhibits mesangial expansion and hypercellularity, with a membranous or endocapillary proliferative pattern. Because of the ultrastructural overlap with cryoglobulinemic GN, an in-depth analysis of clinical data and histomorphology is essential.

In the Hungarian experience, 13 renal biopsy samples with Congo-red negative organized deposits were reinvestigated. The cases were pooled from 5,489 biopsies studied along with immunoglobulin light chains. Eight cases of FGN (incidence 0.15 %) and one case of ITG (incidence 0.02 %) were identified. All the patients were caucasians.

The take-home message is that glomerulopathies with organized deposits may have a similar morphology, but have a quite different pathogenesis. The differential diagnosis of fibrillar deposits in particular may be challenging, and auxiliary methods and clinical information are both required and they should be

Impacting progression and outcomes of DKD:

Translating novel insights with GLP-1 RA to practice

EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIR

Melanie Davies, MD
Leicester, United Kingdom

AGENDA

09:45 – 09:50 **Introduction**
Melanie Davies, MD – *Leicester, United Kingdom*

09:50 – 10:05 **Importance of protection and prevention in cardiorenal disease**
John Deanfield, MD – *London, United Kingdom*

10:05 – 10:20 **The science behind vascular and renal benefits of GLP-1 receptor agonists**
Filip Krag Knop, MD – *Copenhagen, Denmark*

10:20– 10:35 **Clinical outcomes of GLP-1 RA in kidney disease: Current evidence and ongoing trials**
Frederik Persson, MD – *Copenhagen, Denmark*

10:35 – 10:45 **Discussion**
All faculty

SATURDAY, JUNE 15, 2019 | 09:30 – 10:45 HRS | HALL F1

Supported by an unrestricted educational grant from Novo Nordisk.

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thoroughly integrated via an algorithmic approach. A promising new biomarker for FGN is emerging which appears to solve the diagnostic problems. In our experience, the incidence of FGN and ITG is extremely rare in the Hungarian population.

Acknowledgements: Béla Iványi MD DSc (University of Szeged), Attila Fintha MD PhD, Magdolna Kardos MD (Semmelweis University), Tibor Vas MD PhD (University of Pécs) and László Bidiga MD PhD (University of Debrecen) all participated in this retrospective study. The DNAJB9 reactions were provided by Jan Ulrich Becker MD (University of Cologne). ◘

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CEPD 7
Nephropathology course
Thursday, 08.45–17.00, Hall A3

EDUCATION

Diabetic nephropathy versus kidney diseases in diabetics

The emerging role of precision medicine

LORETO GESUALDO
Bari, Italy

Diabetes affects over 400 million people worldwide (8.5 % of the entire population) and this number is expected to rise rapidly (Figure 1). In 2017 diabetes caused 4 million deaths worldwide, mainly due to its related complications. Approximately one in three patients with diabetes develops renal damage, mostly but not only represented by diabetic nephropathy, the primary cause of end stage renal disease (ESRD). Furthermore, patients with diabetic nephropathy (DN) have an increased morbidity and mortality from cardiovascular disease.

Along with the current impossibility of improving risk stratification in normoalbuminuric patients, extensive evidence shows that DN is not the only renal complication of type 2 diabetes (T2D), and kidney biopsy remains the diagnostic gold standard. Diabetic patients with rapidly worsening renal disease are often 'clinically' labeled as having DN, whereas, in many cases, they are rather developing a non-diabetic renal disease or mixed forms. Renal biopsy might be fundamental to clarifying the epidemiology of renal disease in diabetics and for planning proper therapeutic management thus influencing prognosis.

The earliest clinical signs of DN, including persistent urinary excretion of albumin and a temporary increase of the glomerular filtration rate along with the presence of hyperglycemia, cannot identify high-risk progressors, rendering DN prevention still unsuccessful. There is an increasing body of evidence showing that selection of specific omic biomarkers and clinical phenotypes may lead to a better stratification of a patient's specific renal damage in T2D and allow the identification of progressors or responders to a specific therapy. To accomplish this task, however, there is an urgent

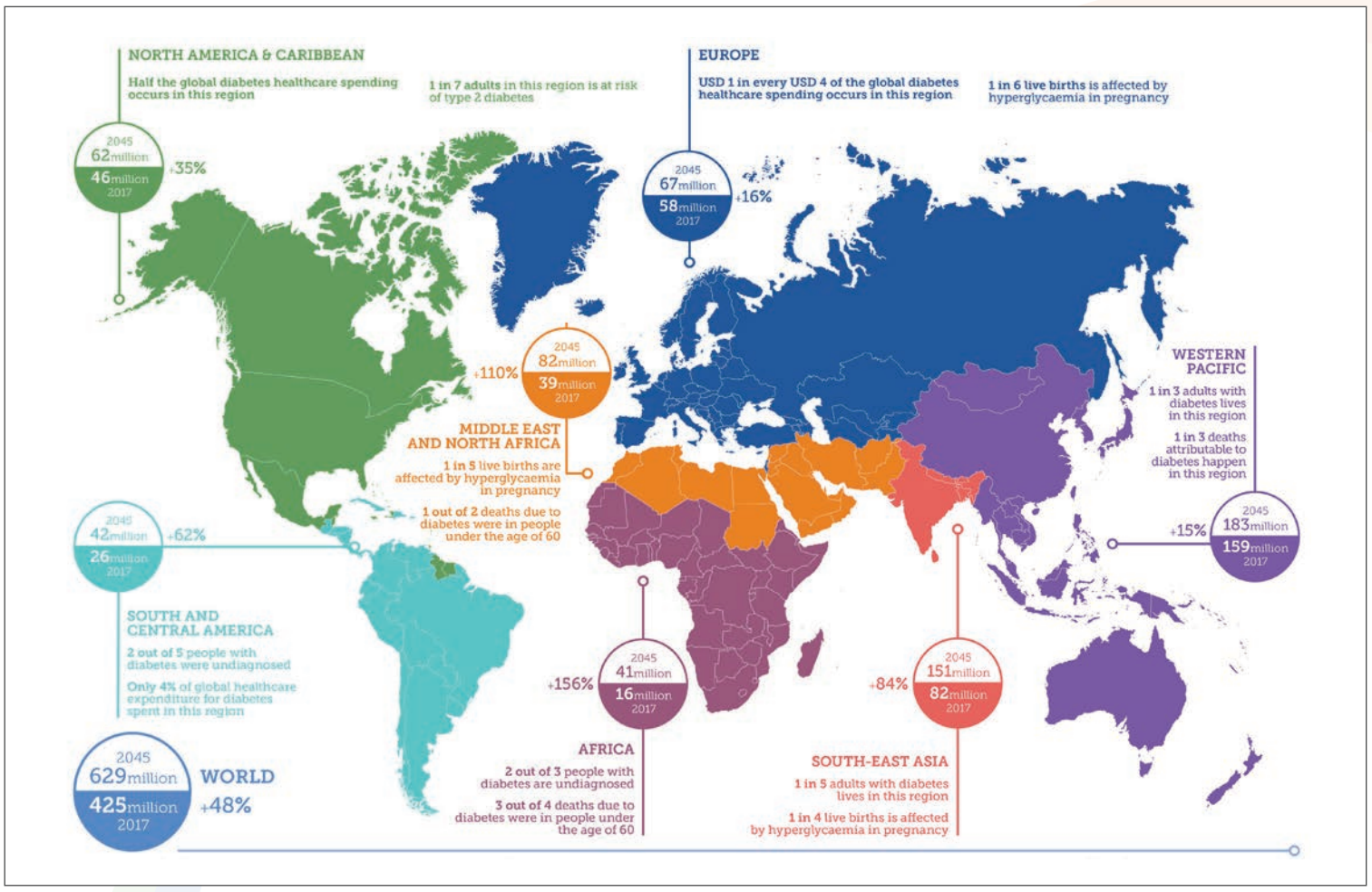

Figure 1: Global estimates of type 2 diabetes prevalence From International Diabetes Federation. IDF Diabetes Atlas, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. © IDF. Courtesy of IDF

need to build up disease-specific platforms containing personal, clinical, and omics profiles that will allow the full potential application of systems biology analysis and the development of specific disease phenotype models.

The term "precision medicine" was introduced with the goal of creating a "new taxonomy of human disease based on molecular biology" to replace the classical descriptive diagnostic terms [1]. The goal of precision medicine is today to characterize disease based on the molecular biology signature, in order to identify specific biomarkers and therapeutic targets that will improve clinical outcomes of patients. Although a large number of biomarker candidates for DN have been described, most of these studies are too small to be definitive and need longitudinal validation.

Precision medicine has the goal of tailoring medical treatments according to the patient's individual characteristics. It focuses on the specific classification of patients into subgroups with different susceptibility to a particular disease, on the identification of biological processes involved in disease development, and on the individual response to a specific treatment. All these goals are today more reachable thanks to the development of novel high-throughput technologies.

Precision medicine in diabetic kidney damage has the goal of developing non-invasive molecular markers to identify true diabetic nephropathy from non-diabetic renal disease or mixed forms in diabetic patients. ◘

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CEPD 7
Nephropathology course
Thursday, 08.45–17.00, Hall A3

EDUCATION

Different flavors in RCTs and their analysis How RCTs can help decision making in routine practice

GIOVANNI TRIPEPI
Reggio Calabria, Italy

Randomized clinical trials (RCTs) are considered the gold-standard study design for testing the intended effect of a therapy on a given pathophysiological pathway to prove causality. In an RCT, the clinical benefit of a specific intervention on a given binary outcome (for example death, fatal and non-fatal cardiovascular events, end-stage kidney failure, etc.) is assessed by relative (risk ratio, odds ratio, incidence rate ratio, and hazard ratio) and absolute (risk difference) measures of effect, as well as by measures of clinical impact, such as the number needed to treat (NNT, which is derived from the risk difference). Another aim of an RCT is to provide safety information on the treatment being investigated. The number needed to harm (NNH) and the likelihood to be helped or harmed (LHH – i.e. the ratio between NNH and NNT) are two indexes that can be calculated to assess the risk/benefit balance of a given drug.

When reading an RCT it is also important to correctly interpret a Kaplan-Meier (KM) survival curve, which plots the cumulative event-free survival as a function of time. Assessing differences between two similar KM survival curves can pose a challenge for clinicians without training in statistical data analysis and interpretation. For this reason, there has been an increased reliance on hazard ratios, often to the exclusion of more traditional survival indexes. However, because a hazard ratio lacks dimensions, it can only inform the clinician about the reliability and uniformity of the survival data. The hazard ratio does not provide practitioners with quantitative values they can use, nor does it provide information they can discuss with patients. Furthermore, two RCTs of different drugs impacting upon the same pathophysiological pathway can display identical hazard ratios, but we cannot take for granted that the clinical impact (i.e. in terms of NNT) is the same for the two drugs being investigated.

For dichotomous outcomes (such as death, myocardial infarction, etc.), the hazard ratio is defined as the hazard in the exposed groups divided by the hazard in the unexposed groups. For all practical purposes, hazards can be thought of as incidence rates and for this reason the hazard ratio can be roughly interpreted as the incidence rate ratio. The hazard ratio is commonly and conveniently estimated via the Cox proportional hazards model, which can include potential confounders as covariates (i.e. prognostic variables that differ between the two study arms by chance). Very often, in an RCT a forest plot is used to show the effect of the experimental drug on study outcomes by strata of relevant variables. This type of analysis is important to identify potential effect modifiers.

During the talk, by using real examples, I will discuss the concepts of relative and absolute measures of effect. I will also describe how to derive from a given paper, when not directly reported in the results section, further indexes of the clinical impact of a specific drug – indexes that can help the clinician in taking decisions in every day clinical practice. ◘

CEPD 9
Renal transplantation
Thursday, 13.00–16.40, Hall G2A

RAASi and hyperkalaemia in cardiorenal disease: Opportunities for optimizing outcomes

EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIRMEN

John Cunningham, MD – *London, United Kingdom*

Matthew Weir, MD – *Baltimore, MD, USA*

AGENDA

09:45 – 09:50 **Introduction**
John Cunningham, MD – *London, United Kingdom*

09:50 – 10:05 **RAAS inhibition in patients with kidney disease: Balancing the benefits and risks**
Patrick Rossignol, MD – *Nancy, France*

10:05 – 10:20 **Addressing the risk of hyperkalaemia: Is there a sweet spot for potassium binding?**
Peter van der Meer, MD – *Groningen, the Netherlands*

10:20– 10:35 **Managing hyperkalaemia in cardiorenal patients: Novel therapeutic insights to optimize outcomes**
Matthew Weir, MD – *Baltimore, MD, USA*

10:35 – 10:45 **Panel discussion & summary**
John Cunningham, MD

SATURDAY, JUNE 15, 2019 | 09:30 – 10:45 HRS | HALL G2B

PACE-CME

Supported by an unrestricted educational grant from Vifor Fresenius Medical Care Renal Pharma.

"In compliance with EBAC guidelines, all speakers/chairpersons participating in this programme have disclosed or indicated potential conflicts of interest which might cause a bias in the presentations. The Organising Committee/Course Director is responsible for ensuring that all potential conflicts of interest relevant to the event are declared to the audience prior to the CME activities."

VIFOR PHARMA

Can this person receive a kidney? What is the minimal workup in a healthy kidney transplant candidate?

era edta DESCARTES working group
Developing Education Science and Care for Renal Transplantation in European States

LUUK HILBRANDS
Nijmegen, The Netherlands

Patients wishing to undergo renal transplantation are subjected to screening procedures to assess their suitability. Existing guidelines on the evaluation and preparation of recipients for kidney transplantation target the entire spectrum of patients with end-stage renal disease.

Within the ERA/EDTA DESCARTES Working group it was proposed that in a subset of relatively young patients (< 40 years) without significant comorbidities (such as diabetes or cardiovascular disease), the work-up for transplantation could be restricted to a small set of tests. A survey on the opinion of 80 transplant professionals from 11 European states showed that there is wide agreement among European experts that the work-up for kidney transplantation of the low-risk candidate, as opposed to the standard risk candidate, could include a limited number of investigations. After comparison with existing guidelines and discussion within the DESCARTES Working group, this led to the proposal for the work-up of young, comorbidity-free kidney transplant candidates as displayed in the Table. There were four additional tests that more than 25 % of the respondents of the survey suggested for inclusion in a standard work-up: abdominal ultrasound, echocardiography, syphilis testing, and ultrasound of the iliac vessels.

However, the DESCARTES Working group considered the supporting evidence too low for recommendation in low-risk patients. Interestingly, disagreement on these items was related to geographic location within Europe and the professional background of the respondents. In general, respondents from the UK, Denmark, and The Netherlands had a more restrictive attitude towards performing screening investigations, while there was a trend by Austrian and Italian respondents to be more exhaustive. In addition, nephrologists were more likely than surgeons to include examinations in the standard work-up.

A limited work-up of low-risk kidney transplant candidates will contribute to a timely listing for transplantation. Physicians and transplant centers striving for cost-effective patient care will hopefully feel supported by the consensus statement from a group of European opinion leaders. ◘

Detailed history and thorough physical examination
Laboratory assays Full blood count, liver enzymes, INR/APTT, HBV, HCV, HIV, CMV, EBV, VZV serology, PTH, urine culture
Other assays/consultations Chest X-ray, ECG, ultrasound of kidneys, cancer screening according to national guidelines, regular dentist visit
To be considered as part of standard work-up Screening for latent infection with Mycobacteria Syphilis testing Review of native kidney biopsy Testing for genetic cause of kidney disease

Table: Recommendations for the work-up of low risk renal transplant candidates

References

01. Maggiore U, et al. Standard work-up of the low-risk kidney transplant candidate: a European expert survey of the ERA-EDTA Developing Education Science and Care for Renal Transplantation in European States Working Group. Nephrol Dial Transplant 2019 Jan 9. doi: 10.1093/ndt/gfy391.

CEPD 9
Renal transplantation
Thursday, 13.00–16.40, Hall G2A

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LEADING EUROPEAN NEPHROLOGY

VISIT our booth at # 820

Don’t miss the opportunity to meet some of our key leaders at the booth: check out their schedule in this issue!

INSTITUTIONAL

Meet the ERA-EDTA Leaders at the ERA-EDTA Booth

Carmine Zoccali

Don't miss the opportunity to meet and network with ERA-EDTA leaders at the ERA-EDTA Booth in the Exhibition Area. They will be happy to speak to you about the association, scientific projects, developments in nephrology and related topics. Come with ideas as well as with criticism – our leaders will have an open ear for you. "We believe that a two-way communication with our members is essential. It is not only about informing the members and giving information, but also about receiving feedback and discussing various issues with our members", explains Professor Carmine Zoccali, President of the ERA-EDTA. Here is the full schedule, when to meet whom.

Friday, June 14

Prof Marten Segelmark, IWG Vice Chair: 9.30–10.30
Prof Jonathan Fox, ERBP Chair: 9.30–10.30
Dr Evi Nagler, ERBP Vice-Chair: 9.30–10.30
Prof Denis Fouque, Editor in Chief NDT: 10.00–11.00
Prof Francesca Mallamaci, EURECA-m Chair: 10.00–11.00
Prof Carsten Wagner, SAB Vice-Chair: 10.30–11.30
Dr Esteban Porrini, Diabesity Chair: 11.00–12.00
Prof Marc Vervloet, CKD-MBD Chair: 11.30–12.30
Prof Francesco Schena, Ethics Commitee Chair: 13.30–14.30
Prof Sandro Mazzaferro, CKD-MBD Vice Chair: 14.00–15.00
Prof Daniel Teta, ERN Vice Chair: 15.00–16.00
Prof Kitty Jager, ERA-EDTA Registry Managing Directory: 15.00–16.00
Prof Ivan Rychlík, Secretary-Treasurer: 15.00–16.00
Prof Nine Knoers, WGIKD Chair Elect and current Vice Chair: 16.00–17.00

Saturday, June 15

Dr Carlo Basile, EUDIAL Chair: 9.30–10.30
Prof Luuk Hilbrands, Descartes Chair: 10.00–11.00
Prof Danilo Fliser, Renal Science Chair and Chairperson of the Administrative Offices: 11.00–12.00
Dr Davide Bolignano, Editor in Chief NDT-Educational@ENP: 11.00–12.00
Dr Kate Stevens, ECC Chair, YNP Chair: 11.00–12.00
Prof Vladimir Tesar, IWG Chair: 11.30–12.00
Prof Juan Jesus Carrero, ERN Vice Chair: 13.30–14.30
Prof Charles Ferro, EURECA-m Vice Chair: 14.00–15.00
Prof Alberto Ortiz, Editor in Chief CKJ: 15.30–16.30

EDUCATION

The interplay and interaction between frailty and AKI
Potential mechanistic links and the effect of frailty on outcomes

NORBERT LAMEIRE
Ghent, Belgium

Vulnerability to stress, or homeostenosis, is a well-known aspect of natural aging. By comparison, 'frailty' is "a separate and distinct state of exaggerated vulnerability and poor resolution of homeostasis following a stress", with more clinically meaningful drivers and outcomes, although it may be misattributed to chronologic age. 'Frailty' is defined as a phenotype where "one's physiological reserve differs significantly from one's biological age". Frailty comprises domains such as nutritional status, energy expenditure, metabolic rate, cognitive function and sarcopenia, and occurs most frequently in older adults. It carries high risk of poor outcomes such as physical disability, frequent hospitalizations, functional decline, falls, health services use, and subsequent institutionalization, particularly in critically ill elderly patients admitted to the intensive care unit (ICU).

Frailty is considered to be an emerging public health priority, is a common trajectory in late life, and perhaps the most problematic expression of population aging.

Several clinical tools have been developed to help in the diagnosis of the frailty syndrome. The most commonly used are:

1. The Physical Frailty Phenotype (PFP), which identifies frailty phenotypes based on the examination of changes in weight, weakness and walking speed.
2. The Comprehensive Geriatric Assessment (CGA), which examines medical, psychosocial, and functional limitations of older adults by a multidisciplinary team of healthcare professionals, with the objective of creating a treatment plan of long-term support and rehabilitation for frail adults.
3. The Clinical Frailty Scale (CFS), which uses pictographs to subjectively stratify older adults according to their level of vulnerability to poor outcomes such as prolonged hospitalizations and increased mortality.

In the ICU, the most popular evaluation of frailty is based on the multidimensional model proposed by Rockwood et al [1]. This model considers frailty to be an accumulation of deficits in various domains, and frailty can be determined by the calculation of a frailty index. The details of each item (up to 70 items) included in the frailty index are unwieldly in clinical practice, and measurement of frailty by the CFS is now widely used, notably in the ICU. This scale is based on a clinical examination, the patient's medical record, and an interview with the patient or proxy(ies) if the patient is not able to be interviewed.

To date, most frailty studies have evaluated frailty in patients with end-stage kidney disease (ESKD). In ESKD patients, for example, the prevalence of frailty ranges from 35 % to 73 %, and frailty is associated with higher mortality rates.

Acute kidney injury (AKI) frequently complicates critical illness and is associated with high morbidity and mortality. Frailty is common in critical illness survivors, but little is known about the impact of AKI. Although frailty and AKI are commonly encountered in critically ill and elderly patients, their interplay and interaction remain unclear. Nonetheless, it is possible that they predispose to each other in a vicious circle and therefore worsen the patient's overall prognosis [2].

Baek et al [3] determined the effect of frailty as a predictor of AKI. They retrospectively enrolled 533 hospitalized elderly patients (aged > 65 years), who had their creatinine levels measured during admission for a period of one year (2013) and conducted a CGA within one year before the index hospitalization. The authors examined five variables (activity of daily living [ADL] and instrumental ADL dependence, dementia, nutrition, and polypharmacy) from the CGA. Patients were categorized into three groups according to the tertile of aggregate frailty scores: Group 1, score 1–2; Group 2, score 3–4; Group 3, score 5–8). Fifty-four patients (10.1 %) developed AKI (median duration, four days). The frailest group (Group 3) showed an increased risk of AKI as compared to Group 1, (hazard ratio [HR] = 3.536, P = 0.002). The discriminatory accuracy for AKI improved with the addition of the tertile of aggregate frailty score to covariates. Forty-six patients (8.6 %) were transferred to nursing facilities and 477 patients (89.5 %) were discharged home. The overall 90-day and one-year mortality for elderly inpatients was 7.9 % and 26.3 %, respectively. The frailest group also demonstrated an increased risk of discharge to nursing facilities, and 90-day and one-year mortality as compared to Group 1, independent of AKI severity. That study suggests that frailty may independently predict the development of AKI and adverse outcomes in geriatric inpatients.

Morton et al [4] assessed whether an individual's (CFS score was associated with AKI in acute elderly medical admissions and whether it was associated with short-term outcomes. Of 164 patients (77 males), 19 % had AKI on admission and 22 % were considered severely frail. Severe frailty was associated with AKI (P = 0.01) and death within two weeks (P = 0.01). Two-week mortality was highest among patients with both severe frailty and AKI (36 %). The incidence of AKI in 'severely frail', acutely unwell elderly patients is thus significantly higher and associated with an increased short-term mortality. In this study, the CFS was useful in acute illness to guide clinical decisions in elderly patients.

Abdel-Kader et al [5] performed a retrospective study using data from a multicenter prospective study (BRAIN-ICU study in five medical centers), which included adults ≥ 18 years old who had acute respiratory failure and/or septic or cardiogenic shock. The study was limited to a cohort of patients evaluated in one center where the daily serum creatinine level was available. For this purpose, the authors used a careful estimation of the baseline serum creatinine level and AKI was staged according to the Kidney Disease Improving Global Outcome (KDIGO) guideline. Frailty was classified according to the CFS, which was determined during the first 72 hours of hospitalization in the ICU, as well as in survivors at three and six months after discharge from the hospital. Covariates included mean ICU sequential organ failure assessment (SOFA) score and acute physiology and chronic health evaluation II (APACHE II) score as well as baseline comorbidity (i. e. Charlson Comorbidity Index), kidney function, and CFS score. Of 317 patients, 243 (77 %) had AKI and one in four patients with AKI were frail at baseline. In adjusted models, AKI stages 1, 2, and 3 were associated with higher frailty scores at three months. At 12 months, a similar association of AKI stages 1, 2, and 3 and higher CFS score was noted and in supplemental and sensitivity analyses, analogous patterns of association were observed. It was concluded that AKI in survivors of critical illness predicted worse frailty status three and 12 months post-discharge. These findings have important implications on clinical decision making among AKI survivors and underscore the need to understand the drivers of frailty to improve patient-centered outcomes.

As noted in an editorial commentary on the study of Abdel-Kader et al [6], the association between AKI and frailty decreased with time. Since there is no data regarding the level of kidney recovery at three and 12 months in the Abdel-Kader study, it is notably that in patients who had persistent AKI at discharge from the hospital, it is difficult to determine whether frailty was preferentially present in patients who maintained a chronic renal dysfunction. Additionally, the incidence of AKI during an ICU stay was 77 %, and 27 % of patients were discharged from the hospital with

some degree of AKI, which may be explained by the type of patients included in the study and raises the question whether these results can be generalized to all ICUs.

Frailty can often be seen in high-risk patients undergoing transcatheter aortic valve replacement (TAVR). Preoperative frailty status is thought to be related to adverse outcomes after TAVR. A recent systematic literature study [7] reported on databases on the association of frailty status with AKI and mortality after TAVR. Studies that reported odds ratios, relative risks or hazard ratios comparing the risk of AKI after TAVR in frail versus non-frail patients were included. Mortality risk was evaluated among the studies that reported AKI-related outcomes. Pooled risk ratios (RR) and 95 % confidence interval (CI) were calculated using a random-effect, generic inverse variance method. Eight cohort studies with a total of 10,498 patients were identified and included in the meta-analysis.

The pooled RR of AKI after TAVR among the frail patients was 1.19 (95 % CI 0.97 ± 1.46, I2 = 0), compared with non-frail patients. When the meta-analysis was restricted only to studies with standardized AKI diagnosis according to Valve Academic Research Consortium (VARC)-2 criteria, the pooled RRs of AKI in frail patients was 1.16 (95 % CI 0.91 ± 1.47, I2 = 0). Within the selected studies, frailty status was significantly associated with increased mortality (RR 2.01; 95 % CI 1.44 ± 2.80, I2 = 58). While this study thus suggests no significant association between frailty status and AKI after TAVR, frailty status is associated with mortality after TAVR and may aid appropriate patient selection for the procedure.

A more recent systematic review and meta-analysis determined the impact of preoperative frailty status on outcomes among patients after TAVR [8]. The pooled risk ratios (RRs) of late mortality (> 6 months) and AKI after TAVR in the frail group were 2.81 (95 % CI 1.90–4.15, P < 0.001, I2 = 84 %) and 1.41 (95 % CI 1.02–1.94, P = 0.04, I2 = 24 %), respectively. Compared with the non-frail group, significantly higher incidence of 30-day mortality (RR 2.03, 95 % CI 1.63–2.54, P < 0.001, I2 = 0 %) and life-threatening or major bleeding after TAVR (RR 1.48, 95 % CI 1.20–1.82, P < 0.001, I2 = 14 %) were found in the frail group.

In conclusion, AKI is independently associated with frailty, and the majority of survivors of critical illness complicated by AKI are clinically frail at three and 12 months after discharge. Further research is needed to understand potential mechanistic links and the effect of frailty on outcomes in patients in whom AKI developed during critical illness. Because frailty is associated with functional decline in the critically ill, interventions to maintain independent function among patients who survive AKI are needed. ◘

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CEPD 10
AKI
Thursday, 13.00–16.40, Hall G2B

EDUCATION

Peritoneal infection in PD: an update A task force approach to prevention, diagnostics and treatment

ANABELA RODRIGUES

Porto, Portugal

Peritoneal infection ranks highest in the list of the outcomes that patients fear and prioritize [1]. Clinicians are also aware that peritoneal catheter-related infections menace technique and patient survival, frustrating the opportunity to offer the high-performance dialysis modality of peritoneal dialysis (PD).

A task force approach must be adopted to prophylaxis and quality control, in order to reduce rates of catheter-related infections. This approach begins in the allocation phase with better patient selection and education, but surgical skills and catheter pre-implantation steps are critical [2]. Some strategies with evidence to support their mandatory use to decrease infection rates include: surgical skills, disconnect Y-set systems, pre-implantation intravenous antibiotic prophylaxis, exit–site mupirocin ointment application in at-risk patients. International Society for Peritoneal Dialysis (ISPD) best practice in patient preparation and peritoneal catheter implantation should be followed carefully.

Modifiable risk factors for peritonitis include a broad list of fields for intervention: periluminal infection is related to pre-operative procedures and exit-site early colonization; intraluminal infection is related to connectology and patient training. Transmigration of bacteria across the intestinal wall has been related to several conditions such as hypokalemia, constipation, use of H2-antagonists, and congestive heart failure. Secondary peritonitis after bacteremia (respiratory infection by *Haemophilus influenzae, Streptococcus viridans* peritonitis after dental procedures, as examples) or migration from the genito-urinary or intestinal tract after invasive procedures should be taken into account. Prophylactic antibiotics before invasive gastrointestinal and gynecological procedures, as well as prophylactic oral fluconazole during a course of peritonitis/ESI antibiotic treatment are recommended.

The microbial biofilm in peritoneal dialysis catheters, its characterization and microbial behavior in dialysis fluids are also a relevant field of investigation [3]. Biofilms are communities of microorganisms adherent to a surface and enmeshed in an extracellular matrix of microbial and host-derived components. In contrast to cells in suspension (i. e. planktonic), this protective phenotype enables microorganisms to evade the immune system and to gain tolerance to antimicrobial drugs. Biofilms, highly dominated by Staphylococci and P. aeruginosa, are ubiquitous on PD catheters, although their microbial burden may allow an infective status. Choice of PD solution did not show a conclusive impact on peritonitis rate but may differentially impact microbial biofilms. Aseptic technique and routine substitution of the catheter transfer set are mandatory, while more aggressive therapy under microbiological guidance, instead of routine minimal inhibitory concentrations, might be opportune to overcome the risk of catheter colonization, relapse and repeat peritonitis.

This focused investment to overcome the high drop-out from the modality within the first years of PD is utterly important, but it should be kept in mind that unplanned transfer to hemodialysis (HD) within the first four years of PD [4], mainly associated with catheter-related complications, still does not efface the clinical benefit of a PD-first option. A profile of repeat peritonitis might allow a planned transfer to HD with secure vascular access, optimizing the flux between modalities and protecting global patient survival. Indications for catheter removal include refractory, relapsing or recurrent peritonitis, as well as refractory exit site and tunnel infection, fungal and non-tuberculous Mycobacterium peritonitis. However, simultaneous new catheter reinsertion is feasible in relapsing peritonitis caused by Staphylococcal species if antibiotic therapy resolves abdominal symptoms and the peritoneal cell count is < 100/µL Developments in microbiological diagnostic techniques in peritoneal dialysis, such as culture-independent antimicrobial susceptibility testing and increasing knowledge of immune fingerprinting of peritonitis agents and its pharmacologic blockade, are examples of future perspectives [5,6].

Infection also has other biological dimensions in PD, promoting local recruitment of immune cells that may either cure, or instead, induce chronic inflammation and submesothelial fibrosis [7]. Therefore, immune cell response after the infectious insult may cause deleterious effects in membrane permeability as evidenced by faster small solute transport and a concomitant lower ultrafiltration. Additionally, an infectious episode is a risk factor for residual renal function loss and increase of serum IL-6 as a sign of systemic inflammation. Both systemic and local intraperitoneal inflammation menace clinical outcomes in PD patients.

Improvement of PD outcomes is certainly dependent on knowledge, expertise and continuous quality control in the units, but also depends on the strategic investment of health systems to promote domiciliary therapies with adequate resources. ◘

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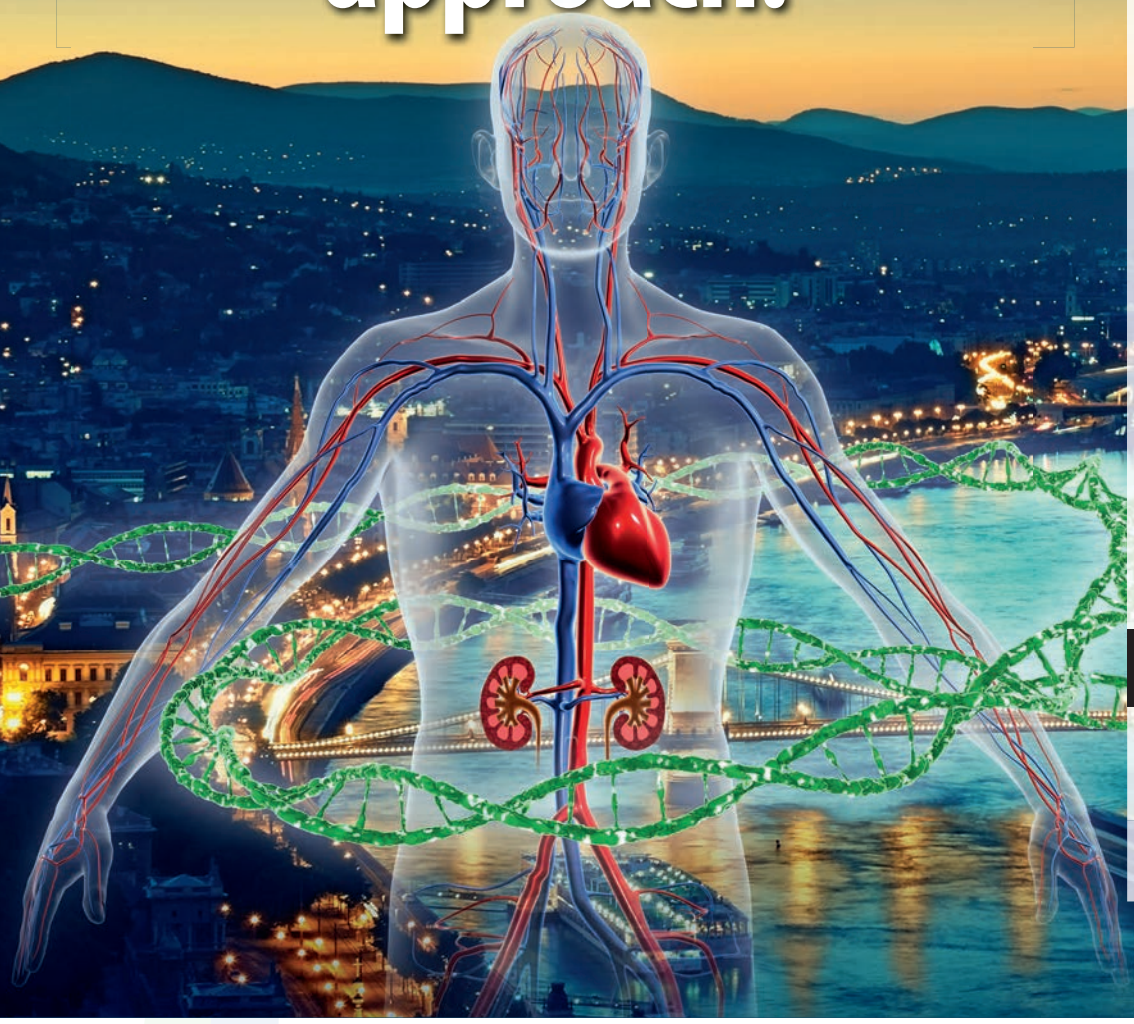
CEPD 11
Peritoneal dialysis
Thursday, 13.00–16.40, Hall F1

Vascular calcification in kidney disease: Epigenetics as a novel approach?



EBAC ACCREDITED SYMPOSIUM TO BE HELD DURING ERA EDTA 2019, BUDAPEST, HUNGARY

CHAIRMEN

Peter Stenvinkel, MD – *Stockholm, Sweden*
Jürgen Floege, MD – *Aachen, Germany*

Lunch will be provided

AGENDA

13:30 – 13:40 **Introduction**
Peter Stenvinkel, MD – *Stockholm, Sweden*

13:40 – 13:55 **Epigenetic mechanisms targeting ALP: A pathway for prevention?**
Marta Ruiz-Ortega, PhD – *Madrid, Spain*

13:55 – 14:10 **The role of ALP as predictor of cardiovascular events and vascular calcification in CKD**
Mathias Haarhaus, MD – *Stockholm, Sweden*

14:10 – 14:25 **Targeting residual cardiovascular risk & vascular calcification: The clinical perspective for BET inhibition**
Vincent M Brandenburg, MD – *Aachen, Germany*

14:25 – 14:30 **Discussion & summary**
Jürgen Floege, MD – *Aachen, Germany*

SATURDAY, JUNE 15, 2019 | 13:15 – 14:30 HRS | HALL A1

PACE-CME

Supported by an unrestricted educational grant from Resverlogix.

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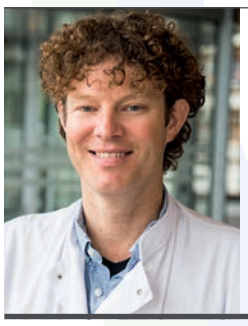
RESVERLOGIX

New developments in vascular access What can we expect for the future?



JORIS I. ROTMANS
Leiden, The Netherlands

Vascular access is the lifeline for patients on hemodialysis. Arteriovenous fistulas (AVFs) are the preferred vascular access modality, but the utility of AVFs is limited by maturation failure that remains a significant clinical problem. Currently, there are no effective therapies available to promote AVF maturation. The pathophysiology of AVF maturation is incompletely understood, but frequently results from venous stenosis at the AVF anastomosis, which is secondary to poor outward vascular remodeling and excessive venous intimal hyperplasia. Recent studies have provided insight in the role of pre-existing vascular pathology, hemodynamic stress, elastin, nitric oxide deficiency and vascular dysfunction as causative factors in AVF non-maturation. In addition, vascular inflammation has emerged as potential contributor, not only to arteriovenous graft failure but also to AVF non-maturation. For instance, studies in murine AVF have shown that marked upregulation of MCP-1 occurs in the venous segment of an AVF that contributes to AVF failure. Another gene of interest involved in AVF remodeling is relaxin, a hormone that stimulates outward remodeling and elastin degradation and suppresses vascular inflammation in murine AVF.

Based on this increased knowledge, various new therapeutic strategies are currently in development and some have been recently evaluated in clinical trials. Recently, clinical trials on the use of liposomal prednisolone and recombinant elastase to promote radiocephalic AVF maturation have been completed. Unfortunately, these interventions did not result in better patency rates of AVF when compared to placebo. Previous randomized controlled trials on anti-platelet agents and fish oil to promote AVF maturation have also largely shown no significant clinical benefit. In addition, various studies aim to modulate the excessive local hemodynamics in AVF by adapting surgical techniques, and several devices are being developed that aim to improve anastomotic flow.

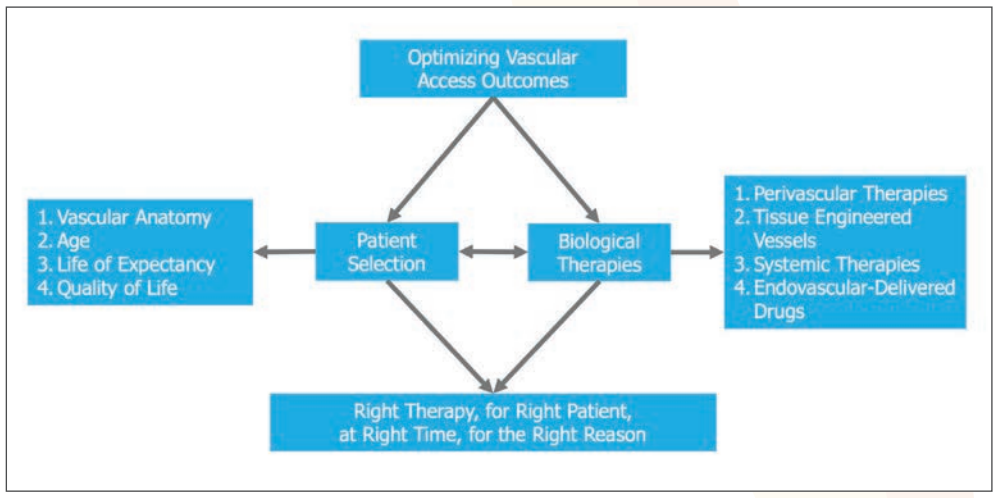


Figure: Personalized approach to optimizing vascular access outcomes. From: Shiu Y-T, Rotmans JI, Geelhoed WJ et al. American Journal of Physiology-Renal Physiology. 15 Apr 2019. https://doi.org/10.1152/ajprenal.00440.2018; permission conveyed through Copyright Clearance Center, Inc.

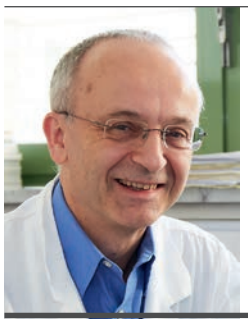
Another emerging field of research in vascular access relates to vascular tissue engineering, which entails the creation of newly engineered blood vessels that can grow, remodel, and repair in vivo. This field is rapidly expanding, with many variations of engineered vascular grafts being employed, some of them already evaluated in clinical trials. Other recent innovations that have entered the clinical field of vascular access are the early-cannulation grafts and the so-called endoAVF, fistulas that are created using an endovascular approach.

Besides these technological innovations, there is an increasing level of consensus that a more patient-centered approach to vascular access for hemodialysis is needed, that incorporates life expectancy, cardiovascular comorbidity, patient preference and quality of life. Such approach implies that an AVF would not be the preferred access type for all patients. During the lecture, the major recent advances in AVF biology will be highlighted, and the results of various preclinical and clinical trials and the concept for a more patient-centered approach to vascular access will be discussed. ◘

CEPD 8
Haemodialysis and vascular access
Thursday, 13.00–16.40, Hall G1

Pre-existing malignancies in renal transplant candidates

DESCARTES working group
Developing Education Science and Care for Renal Transplantation in European States



BRUNO WATSCHINGER
Vienna, Austria

Many physicians tend to be more reluctant to list patients with a history of malignant disease than to accept patients with pre-transplant cardiac events, even though the long-term all-cause mortality risk in these respective patient groups may not differ significantly. A history of malignancy, according to existing guidelines, may lead to a delay in transplantation or to the denial of acceptance to the waiting list.

In preparation for a kidney transplant, potential candidates must undergo pre-transplant screening programs. The presence of an active malignancy is a contraindication for renal transplantation. Patients must be in tumor remission (the time span may vary depending on the type of malignancy) before being considered for transplantation. Increased standardized incidence ratios (SIRs; comparison to the general population) for many types of malignancies do not differ significantly between dialysis and transplant patients. Some types of cancer (mainly attributable to cancers associated with viral infections) occur more often after transplantation. Cancers with particularly higher frequencies after transplantation include Kaposi sarcomas, lymphomas, lip, vulvovaginal, penile and anal carcinomas, and non-melanoma skin cancers.

A high SIR after transplantation should not be the sole reason for withholding a kidney transplant, especially if the SIR for a respective tumor is equally high in a dialysis patient. Staying on hemodialysis carries a five-year cumulative incidence of any cancer of approximately 10 %, indicating that withholding transplantation does not necessarily curtail the malignancy risk for the patient. The fear of potential cancer recurrence is often the reason for delaying transplantation. This potential risk needs to be weighed against the malignancy-independent mortality risk inherent to remaining on long-term dialysis, which is around 5 % per year. Patients should be informed about these different competing risks and be given the opportunity to consent for earlier or later wait-listing and transplantation. Transplants in patients with pre-existing malignancies may be regarded more favorably in countries with a high deceased-donor transplant activity and shorter waiting times than in regions where the waiting times are exceptionally long due to a low number of donor organs. Tumor recurrence rises with increasing time on dialysis, and remaining on dialysis carries an additional mortality risk when compared to being successfully transplanted. Withholding transplantation may thus not be necessarily beneficial for the patient. An appreciation of these competing risks, as well as of novel oncological strategies and genomic profiling data, should be the basis for a thorough interdisciplinary discussion (between oncologists and nephrologists) in every individual patient. An unprejudiced, albeit critical, evaluation may facilitate a reduced waiting time for patients with pre-existing malignancies who wish to receive a kidney transplant. ◘

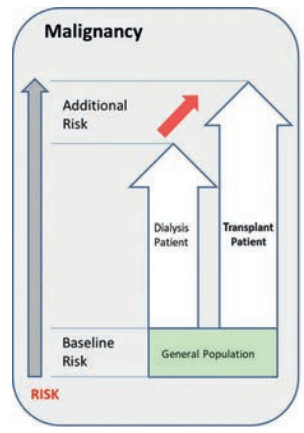


Figure: Risks for malignancy and mortality
From [1]. © NDT. Courtesy of NDT

CEPD 9
Renal transplantation
Thursday, 13.00–16.40, Hall G2A

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EDUCATION

Genomic studies in monogenic and kidney stone disease

JAN HALBRITTER
Leipzig, Germany

Utility of genetic diagnostics in adult chronic kidney disease (CKD) is developing tremendously. As demonstrated by numerous recent publications (e.g. [1]), modern sequencing techniques allow us to study the contribution of heritable disorders in the context of CKD in a fast and cost-efficient manner. One exemplary clinical indication for such diagnostic procedure is end-stage renal disease (ESRD) of undetermined etiology. Despite the discovery of dozens of rare hereditary kidney diseases over the last decades, routine diagnostic work-up does not regularly include consideration of these rare conditions. Additionally, many of these conditions, notably if non-syndromic and non-familial, are hard to diagnose without the use of modern genetics. It is thought that at least 20 % of ESRD patients are listed for kidney transplantation (KT) without a definite diagnosis, in most cases due to missing or unspecific renal histology.

In a pilot study at the University of Leipzig, we attempted to apply a kidney-specific gene panel to cases of undetermined ESRD on the KT-waitlist. As a result, we identified pathogenic variants in 12 % of cases, sufficiently explaining the phenotype. This led to a significant reduction of undetermined ESRD in favor of hereditary ESRD on the total waitlist. Among undetermined cases, the most frequent genetic finding was altered COL4A3–5, followed by pathogenic variants associated with other hereditary glomerulopathies, such as in INF2, PAX2, and WT1. Surprisingly, no case of genetic aHUS/TMA was newly identified on our KT-waitlist [2].

Another clinically important field for the use of modern genetic diagnostics is kidney stone disease and nephrocalcinosis, as these disorders are very heterogeneous and are reported to harbor an estimated heritability of more than 50 %. In a real-world setting, we genetically analyzed an unselected local cohort of 275 consecutive adult patients admitted for endoscopic stone removal by either ureteroscopy (URS) or percutaneous nephrolithotomy (PNL). Underlying molecular genetic diagnoses were found in 6–7 % of cases, affecting genes that contribute to regulation of CaPi-homeostasis (SLC34A1, SLC34A3, CYP24A1), acid-base excretion (SLC4A1), or cystin reabsorption (SLC3A1, SLC7A9). Establishing kidney stone etiology was beneficial when advising patients on adequate prophylaxis and in terms of family counseling.

With these two examples of applied genetic diagnostics, I aim to illustrate the clinical relevance of modern genetics in providing clinicians with an additional diagnostic tool that is most powerful in conjunction with the traditional tools of laboratory, urinalysis, and renal histology. ◘

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CEPD 5
Genetic diseases and rare diseases
Thursday, 08.45–12.25, Hall A1

EDUCATION

Are we inducing adynamic bone disease, and is that a problem? The decision to treat must be based on thorough evaluation of each patient

MATHIAS HAARHAUS

Stockholm, Sweden

Patients with chronic kidney disease (CKD) demonstrate an increased risk of fragility fractures. The underlying causes are complex and represent an interplay of CKD-induced bone pathology with non-CKD specific causes of bone fragility, i.e. primary and secondary forms of osteoporosis. Reduced areal bone mineral density (aBMD) is diagnostic of osteoporosis and treatment-induced improvement of aBMD is associated with a reduction of fracture risk in patients with normal kidney function or mild to moderate CKD. Recently, aBMD was demonstrated to also predict fracture risk in patients with advanced CKD, including dialysis patients, prompting KDIGO to recommend aBMD testing in all stages of CKD, if results impact on treatment decisions. The most commonly used osteoporosis drugs are antiresorptive agents. Their use in advanced CKD has been questioned, largely due to fear of the induction of adynamic bone disease (ABD).

The concept of ABD describes the histomorphometric picture of bone with absent or severely reduced turnover in the presence of normal mineralization. It has evolved as the most abundant form of renal osteodystrophy to date. Aging, diabetes, aluminium-containing phosphate binders, over-suppression of parathyroid hormone (PTH) with calcium or vitamin D, a hypo-responsiveness of bone cells to PTH and osteocyte dysfunction have been suggested as possible causes. Several studies demonstrate associations between low bone turnover, calcium load and arterial calcification. A striking feature of those studies is the association of the syndrome of malnutrition/inflammation with suppressed bone turnover and vascular calcification, which is supported by experimental evidence for a direct inhibitory effect of inflammatory mediators on bone cells. A possible association of ABD with fractures in CKD has been suggested, but evidence is sparse and inconclusive.

Besides active vitamin D and calcium, calcimimetics and parathyroidectomy (Ptx) are PTH-lowering strategies with the potential to severely reduce bone turnover. In addition, both treatment strategies may require calcium and vitamin D supplementation to prevent hypocalcemia. Although no randomized controlled trials of Ptx exist in the dialysis population, a recent large meta-analysis indicates a survival benefit for Ptx compared to medical treatment. No study to date has demonstrated a negative effect of calcimimetics on cardiovascular outcomes, mortality or fractures, in spite of reports on the induction of ABD, if PTH is suppressed below the lower treatment target.

Antiresorptive agents exert their bone-preserving effect through the inhibition of osteoclast and, to a lesser degree, also osteoblast activity, thus resulting in a net increase of bone mass in spite of a reduction of bone turnover. Concerns with bisphosphonates, the first-line antiresorptive agents in osteoporosis, include a possible nephrotoxicity and accumulation with half-lives of up to 10 years for the active substance in advanced CKD. Pharmacokinetics of denosumab, a novel recombinant antibody against receptor activator of nuclear factor kappaB ligand, are independent of kidney function; consequently its use in advanced CKD has increased in recent years. The question whether denosumab is safe in advanced CKD is highly relevant not only due to its potent antiresorptive effect, but also since treatment recommendations to date, in contrast to bisphosphonates, imply the need for continuous treatment, as discontinuation is associated with rebound osteoporosis and increased fracture risk. Both bisphosphonates and denosumab effectively reduce bone turnover markers and increase aBMD in advanced CKD. Several studies in CKD, including dialysis patients, demonstrate that antiresorptive agents do not induce aggravation of vascular calcification, thereby giving additional support to the concept that not all forms of ABD may be harmful to the patient with CKD.

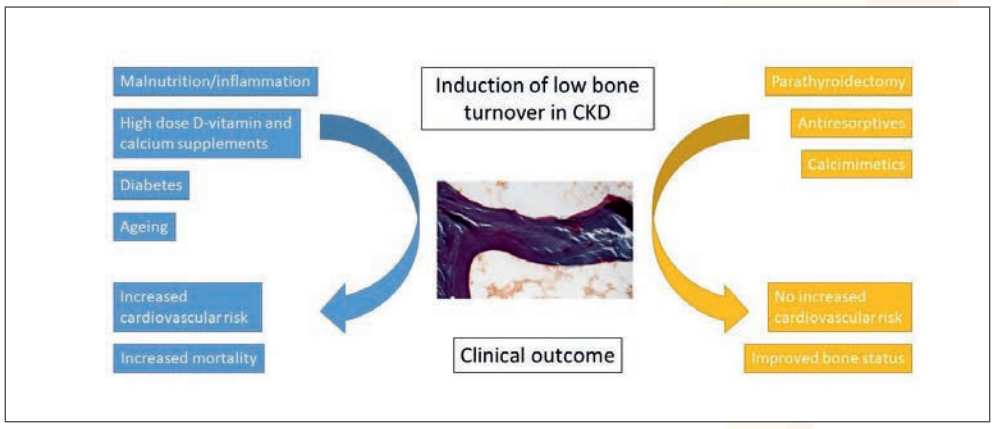

Figure © Mathias Haarhaus

Taken together, low bone turnover per se may not be detrimental in CKD. The underlying cause seems to determine whether low bone turnover puts the patient at increased risk. Based on current knowledge, the decision to treat a patient in CKD 4–5D with low aBMD with antiresorptive agents should thus be based on a thorough clinical evaluation, including clinical risk factors for negative effects of suppressed bone turnover, such as diabetes and the malnutrition/inflammation complex. ◘

CEPD 4
Bone Mineral disorders in CKD
Thursday, 08.45–12.25, Hall F1

EDUCATION

How to prescribe APD A framework to understand the best strategy for each patient

CARL M. ÖBERG

Lund, Sweden

Automated peritoneal dialysis (APD) is a rapidly growing renal replacement therapy that is associated with increased quality-of-life, freeing the patient from the tedious routine of doing manual exchanges, and leaving more time for work, family, and social activities.

This lecture aims to provide a solid foundation in the principles of APD prescription. Despite the complexity of modern APD cyclers, clinical APD prescription for individual patients is simple and straightforward, involving only a few steps. The impact of treatment and dwell time, fill volume and tidal treatments with regard to solute and water clearance will be explained in detail.

Special attention will be given to the possible pitfalls of using dwell time as a parameter in APD prescription. The dialysate flow rate (DFR) is the total treatment volume (in liters) divided by the total treatment time (in hours) and is a more robust parameter in APD prescription. Increasing the DFR will increase small solute clearance and ultrafiltration rate. However, at higher DFRs (>3–4 L/h) the treatment becomes inefficient due to the constant draining and filling of the peritoneal cavity, leaving too little time for effective contact with the peritoneum. Tidal APD means that only part (typically 50–85 %) of an initial fill volume is exchanged for a number of tidal cycles. Tidal APD is associated with increased patient comfort and fewer alarms; somewhat higher efficiency at high DFRs, but slightly less effective at low DFRs compared to non-tidal (full) exchanges [1].

Hands-on advice is given on how to prepare a first APD prescription and important considerations are pointed out. We will then build the framework to understand which patients require special attention and which strategy is the most appropriate. The beneficial effect of APD in patients having fast transport status is well established and suitable clinical strategies for this patient category are discussed. ◘

References

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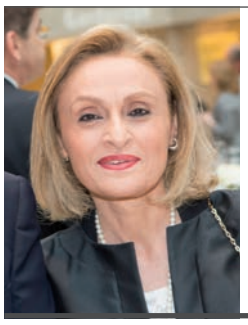
CEPD 11
Peritoneal dialysis
Thursday, 13.00–16.40, Hall F1

EDUCATION

Still on sleep apnea: what can we do?

Sleep-disordered breathing is a pervasive problem in CKD



FRANCESCA MALLAMACI

Reggio Calabria, Italy

Sleep apnea (SA) is a public health problem of paramount importance because it reduces quality of life through disturbed sleep. Snoring is possibly the most common symptom of sleep apnea and it is easily detectable by simply asking the patient's partner or roommates if the patient is snoring when asleep. SA is associated not only with aging but also with obesity, hypertension, heart failure, and diabetes, and it engenders cardiovascular (CV) complications, causing devastating events such as stroke and death.

Sleep alterations are very frequent in stage 5 chronic kidney disease (CKD) patients maintained on regular dialysis treatment. The prevalence of sleep apnea in unselected patients with end-stage kidney disease is over tenfold higher than in the general population, being at more than 50 % in this category of uremic patients. One of the explanations suggested to explain the high prevalence of SA in CKD patients is the accumulation of fluids in some anatomical spaces such as the pharyngeal space, combined with uremic pharyngeal muscle dysfunction.

In a case-control study renal transplantation was shown to reverse SA and in addition to that study, there is other scientific evidence that renal transplantation improves SA in these patients. But although we have enough scientific evidence that renal transplantation improves sleep-disordered breathing (SDB) in cross-sectional observations, the longitudinal, long-term evolution of SDB after kidney grafting has not been fully investigated. The issue is of clinical relevance because in the long term renal transplant patients still have a higher CV risk (although lower than in CKD and in dialysis patients) than their peers in the general population.

The question that we have recently addressed was whether a recurrence or a worsening of SA after renal transplantation could be one of the risk factors in this category of patients. The results of our study in a cohort of renal transplant patients indicate that SA in renal-transplanted patients gradually re-emerges over longitudinal observation. As expected, a rise in body mass index (BMI), a potentially modifiable risk factor, is an important factor underlying the risk of SDB re-emergence. Together with BMI, inflammatory markers such as fibrinogen and CRP are independently associated with SA re-emergence. Therefore contrasting BMI increase and inflammation could be important in tailoring treatment strategy in renal-transplanted patients. ◘

S 04
The many facets of hypoxia in CKD
Friday, 08.00–09.30, Hall F1

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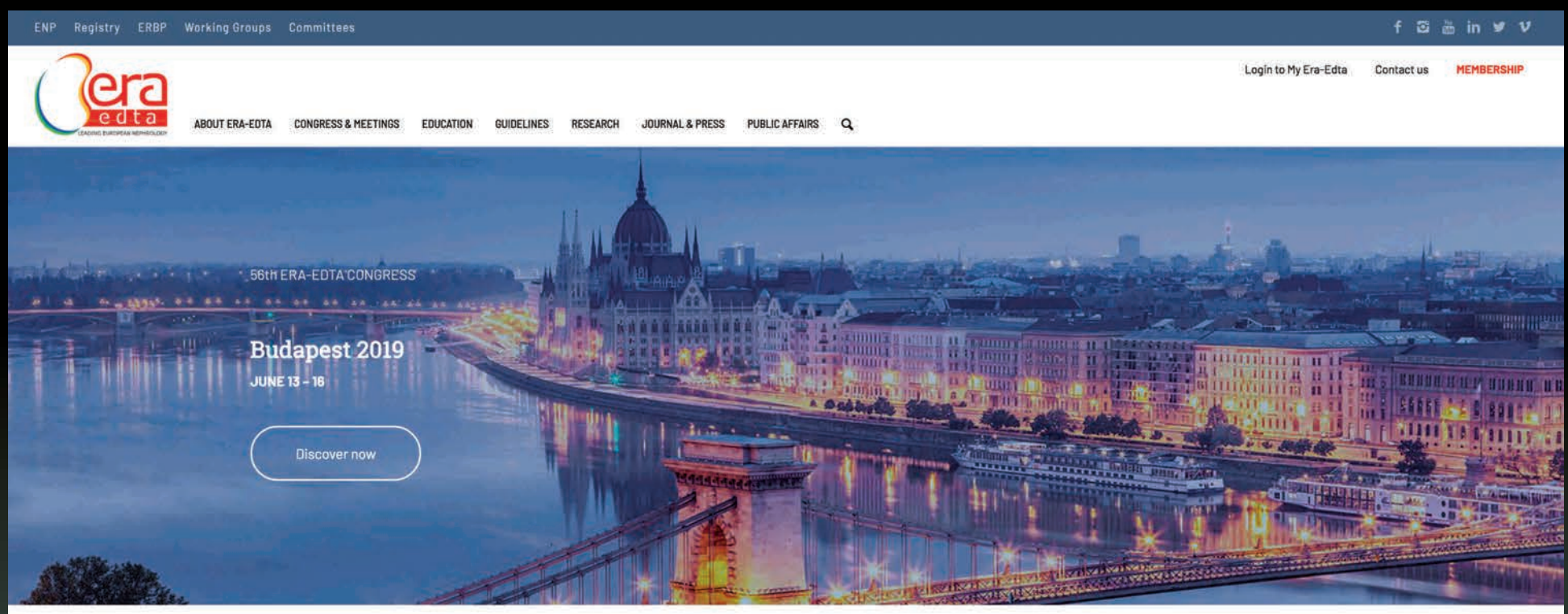

EDUCATION

Factors influencing choice of treatment modality
First results of the European EDITH Nephrologist survey

RIANNE DE JONG

Amsterdam, The Netherlands

The European EDITH project, co-financed by the European Commission, focuses on the differing end-stage kidney disease (ESKD) treatment modalities, as well as on organ donation and transplantation practices, and their impact on health expenditures and patient outcomes (for more information see also www.edith-project.eu).

As part of the EDITH project, the ERA-EDTA Registry surveyed nephrologists and kidney transplant surgeons about factors influencing the choice of treatment modalities for ESKD. In spring 2019, more than 650 professionals from more than 30 European countries responded to the survey.

The first part of this survey covered information provision and decision making, whereas the second part focused on barriers experienced at the patient level (e.g. comorbidity, lack of motivation, unsuitable living circumstances), at the level of the nephrologist (e.g. knowledge or attitude) and at the level of the healthcare system (e.g. lack of skilled staff, insufficient reimbursement, legal barriers). Also, satisfaction about the uptake of all different modalities was investigated. Finally, we collected initiatives in European countries to increase the uptake of different treatment modalities.

We look forward to presenting the first results of the EDITH Nephrologist survey at the ERA-EDTA Registry symposium. It should be noted that, besides the EDITH Nephrologist survey, in 2018 no fewer than 8,100 European dialysis and kidney transplant patients kindly completed the EDITH Kidney patient survey on treatment modality choice. The results from both the EDITH Kidney patient survey and the EDITH Nephrologist survey provide insight into factors influencing treatment modality choice by both patients and doctors. This valuable information could help to improve access to different forms of dialysis, kidney transplantation and comprehensive conservative management in European countries.

We would like to express our gratitude to all participants in the EDITH Kidney patient survey and EDITH Nephrologist survey.

EDITH
The Effect of Differing Kidney Disease Treatment Modalities and Organ Donation and Transplantation Practices on Health Expenditure and Patient Outcomes
Nephrologist survey

The ERA-EDTA Registry very much appreciates that patients, nephrologists and kidney transplant surgeons from almost all European countries shared their experience to improve ESKD care in Europe! ◘

S 01
ERA-EDTA Registry
Friday, 08.00–09.30, Hall G1

EDUCATION

General nephrology and CKD News from
ASN Kidney Week 2018

TAMARA ISAKOVA

Chicago, IL, USA

There are many reasons to be excited about the progress to date and the future in general nephrology and management of chronic kidney disease (CKD). Global accomplishments in CKD recognition and emergence of prognostic tools, exciting results from recent randomized clinical trials of new renoprotective therapies, and ongoing efforts to establish precision medicine approaches in nephrology have moved our field forward, and promise to lead to further developments in therapeutics, changes in clinical practice and improvements in public health.

During the General Nephrology and CKD session at the 2019 ERA-EDTA congress, we will review three important topics covered at the scientific sessions at the ASN Kidney Week meeting in 2018. We will discuss the results from the recently completed BASE clinical trial, review novel approaches to assess kidney function that are based on tubular secretion, and provide an overview of a clinical perspective on management of worsening kidney function in patients with heart failure.

We hope that this session will help attendees stay up-to-date with recent developments, apply new information to the management of their patients and be more sophisticated consumers of the growing scientific literature in the fields of general nephrology and CKD. ◘

S 01
ERA-EDTA Registry
Friday, 08.00–09.30, Hall G1

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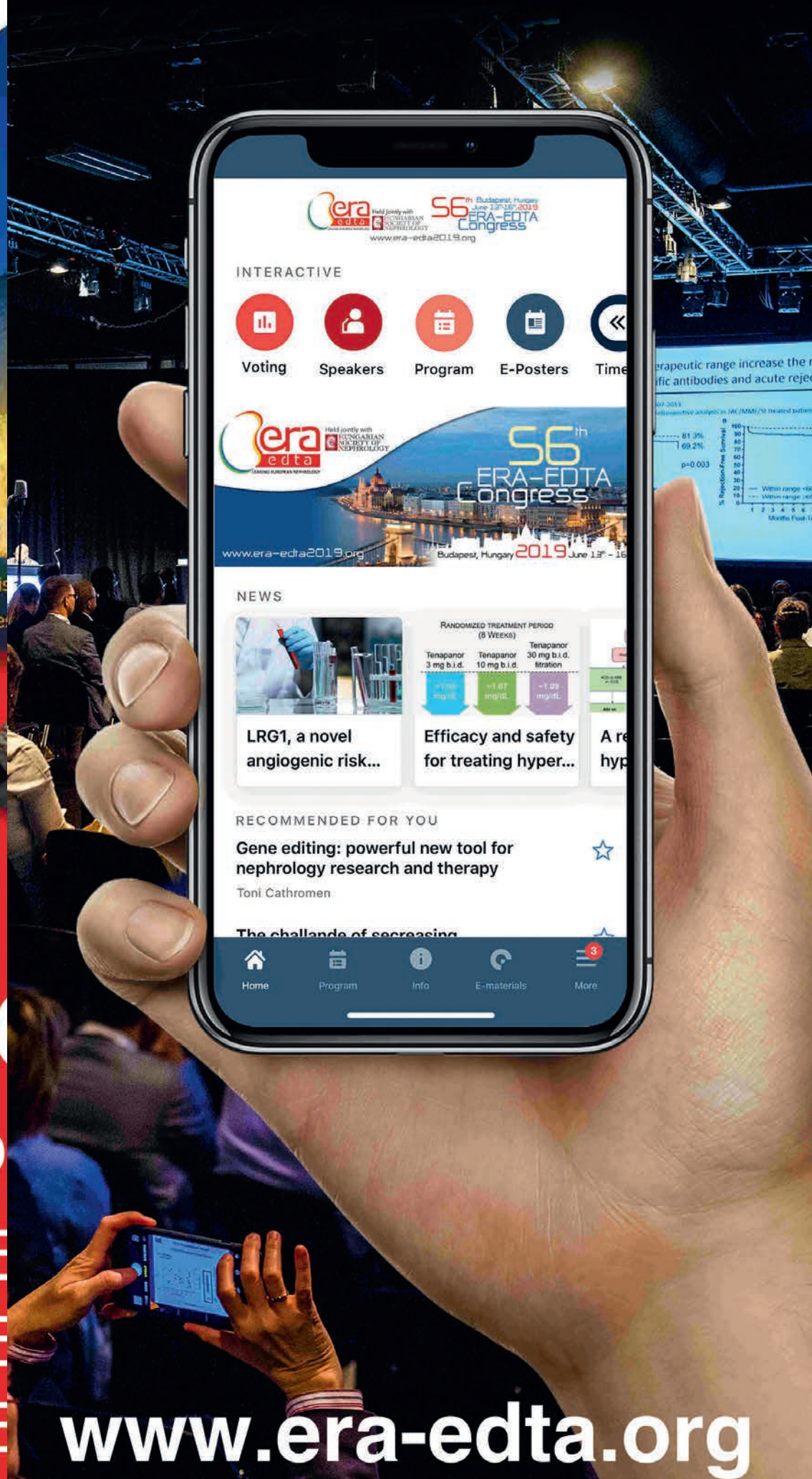

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